THE JOURNAL OF
PEDIATRICS

APRIL 1960 *Volume* 56 *Number* 4

Birth injuries of the spinal cord

Harvey R. Leventhal, M.D.*

NEW HAVEN, CONN.

BECAUSE of better obstetric technique, birth injuries of the spinal cord are not seen as frequently as they were formerly. They do continue to exist, however, as a clinical problem in obstetrics and consequently in neurosurgical management. The entity was first described by Parrot in 1870.[1, 2] He observed an infant, born by a difficult breech delivery, who had signs of transection of the cord and damage to 1 brachial plexus at birth. Little has been written about this subject since the classic work of Crothers, Putnam, and Ford[1, 3-6] in the 1920's when they described 28 infants with paraplegia and discussed the pathogenesis of traumatic breech delivery as the mechanism of injury.

In the general classification of birth injuries, authors usually mention asphyxia, fractures and dislocations, injuries to nerve trunks, and intracranial damage.[2, 7-11] There is scant mention of injuries of the spinal cord and only an occasional warning of the dangers of applying excess traction during delivery.[12-18]

At the Babies Hospital, Columbia-Presbyterian Medical Center, I have had the opportunity of following 6 children ranging in age from 2 months to 12 years with birth injuries of the spinal cord. The youngest child was admitted to the hospital less than 1 year ago with pneumonia. The mother stated that she was unaware of the nature of his spinal lesion. He had been delivered at a well-known hospital. Thus it is worth emphasizing that this type of birth injury still occurs and that it is not merely of historical interest.

The material and patients are from Babies Hospital and Neurological Institute, Presbyterian Medical Center, New York.

Presented at the Southern Neurosurgical Society meeting, Miami Beach, Fla., January, 1959.

**Present address, Department of Neurosurgery, Grace-New Haven Hospital, New Haven, Conn.*

CASE HISTORIES

Case 1 (No. 136-89-09). A 2-month-old child was admitted May, 1958, because of a

Fig. 1. Free flow of dye past site of cord disruption at C-7.

high fever for 24 hours. The child was born by a full-term, difficult breech delivery. No resuscitation was necessary, but the child had flaccid extremities on postnatal examination. Mental development appeared normal. The day prior to admission, fever, cough, and respiratory symptoms developed. The temperature at the time of admission was 101° F., and the pulse, 90; coarse rhonchi were heard in the lung fields and respirations were entirely diaphragmatic. Neurological examination revealed normal strength in the upper extremities with a flaccid paraplegia of the lower extremities and abdominal muscles. Anesthesia was present below T-2. No anal reflex was present. The cranial nerves were normal. There was a weak and feeble cry which could be strengthened by applying pressure to the abdomen thereby giving abdominal muscle fixation. Abdominal pressure also caused bladder and bowel evacuation.

Roentgenograms of the vertebral column were normal. Blood count and nonprotein nitrogen were normal. Spinal fluid protein obtained at myelography was 54 mg. per cent, with 3 white blood cells. On myelography (Fig. 1) the dye flowed readily to the high cervical area. At the C-7 to T-1 level a band radiolucency which extended straight across the Pantopaque shadow was seen. The cord shadow was visible to C-7 but not below, and it was believed that the radiolucent band was produced by an adhesive process without causing an obstruction at the site of disruption of the cord.

Decompressive laminectomy was not indicated and the child was discharged with the suggestion that he be maintained on prophylactic antibiotics as a precaution against urinary tract infection.

Case 2 (No. 307501). A 9-week-old infant was admitted in November, 1956, with a history of lack of movement of the lower extremities and of the right arm since birth. Diagnosis upon admission was "diffuse brain damage as a result of birth trauma." The child was born following a difficult version from face to breech presentation. The labor lasted almost 24 hours; the infant was cyanotic and required resuscitation. On examination at the time of admission, she followed light with her eyes but could not support her head. She held the right arm flexed with the wrist dorsiflexed and the fingers clenched. The breathing was entirely diaphragmatic, and the abdomen was bulging. The lower extremities were flaccid with occasional extensor spasms of the legs on repetitive stimulation, but this was unaccompanied by any objective painful reaction. The reflexes were symmetrical and slightly more active in the lower extremities with a bilateral Babinski response. A sensory level to pinprick was obtained at C-8 to T-1. The diagnosis was physiologic transection of the spinal cord and stretch injury of the right brachial plexus due to birth trauma.

Roentgenograms of the vertebral column were normal as was an electroencephalogram. Chronaxie studies revealed denervated fibers of the right upper extremity consistent with a lower motor lesion at C-6 to T-1. On

the left there was some minimal denervation of fibers in the intrinsic muscles of the hand. The legs showed a normal response. A laminectomy was carried out from C-5 to T-1. The dura mater was thick and adherent to the arachnoid. A cyst was opened in the cord, where it was seen that atrophy of the cord was almost complete. Postoperatively no change in the patient was observed.

Follow-up. The child died of pneumonia at another hospital 2 weeks after discharge.

Case 3 (No. 21-56-18). A 10-month-old girl was admitted in March, 1954, with a history of inability to move her legs since birth. The child was born by a full-term breech delivery and weighed 7 pounds. Labor lasted only 80 minutes. The membranes ruptured before the mother arrived at the hospital and when she was first examined the legs and lower abdomen of the infant had already been delivered. According to the mother, delivery then was completed rapidly, but the details are unknown. The child cried immediately but weakly. No voluntary movement of the legs occurred, but there were occasional flexor or extensor motions to stimuli. During examination on admission a weak cry and diaphragmatic breathing were noted. The abdomen was pendulous and there was a flaccid paraplegia and definite weakness of the paraspinal musculature. The strength in the arms was good. The reflexes in the upper extremities were normal, but there was marked hyperreflexia in the lower extremities with no Babinski response. On painful stimulation, the legs were withdrawn but no effective response to pain occurred until the T-2 dermatome was reached.

Fig. 2. Complete block at site of cord injury.

Roentgenograms of the vertebral column were normal as was an electroencephalogram. Psychometrics gave an indication of average mental development with obvious retardation in physical performance. The iodine test (for starch) showed the absence of sweating below the infraclavicular level. Denervation of fibers in the thumb muscles on the left indicated a level of C-8 to T-1 by electrical studies. Lumbar puncture revealed a slightly xanthochromic fluid with a complete block to manometric techniques. The spinal fluid protein was 600 mg. per cent. Myelography showed a complete block at T-1 (Fig. 2). Laminectomy was performed from C-7 to T-2 and there were numbers of firm epidural adhesions when the lamina was removed. The dura mater, which was 0.5 cm. thick, was very adherent to the remnants of the cord and no normal structure of the cord could be seen. There was no improvement postoperatively. Repeat roentgenograms, however, revealed that the previously seen complete block at myelography was relieved as shown by the presence of dye in the basal cisterns.

Follow-up. On examination at the age of $3\frac{8}{12}$ years, there had been no further recovery of the lower extremities in either motor or in sensory spheres. Crude testing indicated normal intelligence. She continued to have sporadic fevers in warm weather but no longer had the wide swings of variation

in temperature despite the fact that she did not perspire below the level of the chest. Evacuation of the bladder was complete by Credé's method. Intravenous pyelograms performed at yearly intervals have shown no evidence of hydronephrosis. The child at present is receiving physiotherapy and can ambulate with long leg and torso braces though she usually finds it easier to use a wheel chair.

Case 4 (No. 917273). A 15-month-old infant was transferred from another hospital in July, 1948, with a diagnosis of "congenital incomplete development of the nervous system possibly accompanying muscular dystrophy." The child was born by a full-term breech delivery which was described as "very difficult." Directly after birth paralysis of both arms was observed but no mention was made of paraplegia.

During examination on admission it was noted that the child was poorly developed; she could not hold up her head or sit. Her temperature was 104° F. There was some facial asymmetry. The lungs had coarse rhonchi and on respiration there was flaring of the costal margins. The left arm was held rotated externally and weakness of the muscles of the upper extremities, neck, and back was seen. Reflexes were symmetrical but slightly more active in the legs than the arms and there was a bilateral Babinski response. Sensation was recorded as normal. The cranial nerves were intact except for a slight left Horner's syndrome.

Roentgenograms of the skull and vertebral column were normal. There was a healed fracture in the outer third of the right clavicle. Lumbar puncture without manometric measurements revealed no cells, a protein level of 22 mg. per cent, and a sugar level of 57 mg. per cent. The iodine test (for starch) confirmed the fact that there was no sweating below T-2. This was thought to be due to "ectodermal dysplasia" and a skin biopsy was performed which showed a scarcity of sebaceous glands, sweat glands, and hair follicles.

Several days had passed before it was realized that the child was anesthetic to pinprick below T-2 and parapelgic, and the movement which ensued was a reflex rather than from pain. She was discharged with a diagnosis of bilateral brachial plexus stretch injury and birth injury of the spinal cord.

Follow-up. The mother states that at age 10 the child is almost 5 feet tall and weighs 110 pounds. She gets about well in a wheel chair and has normal mentality. Crutches cannot be used because of persistent weakness of the arms. The child now perspires below the waist though there was a previous negative iodine test (for starch) below T-2. Bladder and bowel function are under volitional control during the day but at night she is frequently incontinent. Scoliosis which progressed over the years and was uncontrolled by braces was treated by a spinal fusion from C-5 to L-3.

Case 5 (No. 85-27-32). A 4-month-old boy born in August, 1946, was admitted to the hospital with a history of inability to move his legs since birth. His full-term breech delivery was reported by the obstetrician to have required a great deal of force. Weight at birth was 6 pounds, 6 ounces. No movement of the legs was observed and he was placed in a respirator because of respiratory difficulty.

On examination at the time of admission the child was alert, had a good sucking reflex, and could follow light and objects with his eyes. He supported his head and had a normal respiratory mechanism including good use of the intercostal musculature. The upper extremities were intact but there was a spastic paraplegia of the lower extremities. The hips were abducted and rotated externally, the knees were flexed, and the feet were in the equinus position. There was a lumbar scoliosis to the left. Occasional downward thrust of the foot was obtained when the patellar tendon was tapped. The upper abdominal reflexes were present while the lower abdominal and cremasteric reflexes were absent. Anesthesia was complete below the T-12 dermatome. The bladder emptied completely with no interim dribbling. Roentgenograms of the vertebral column were normal. On lumbar puncture there was no block

to manometric maneuvers and the spinal fluid protein level was 33 mg. per cent.

Lesions at the thoracolumbar area due to birth injuries are uncommon but have been reported.[5] This child had a paraplegia, sensory level, and a nonprogressive lesion; this fulfilled the criteria of birth injury.

Follow-up. The child is now 12 years old, weighs 80 pounds, and is 4 feet, 7 inches tall. He has graduated from the sixth grade, appears to be of good mentality, and has adjusted to his physical handicap. He has no difficulty with his arms but the motor and sensory levels remain at T-12. Some spontaneous extensor spasms of the legs occur. He uses a leg urinal and has no control of the bowels but recently has noted some low abdominal sensation when defecating. There has been one episode of urinary tract infection which was treated with antibiotics.

Case 6 (No. 801439). A 5½-month-old infant was admitted in March, 1946, with a history of frequent high febrile attacks. A broken clavicle was evidence of a difficult breech delivery. Weight at birth was 8 pounds. At home it was thought that the child had occasional spontaneous movements of the legs. On physical examination the temperature was 100° F. She had an apathetic cry and attempts to cough were very feeble. There was prominent flaring of the lower ribs accompanied by diaphragmatic breathing. The abdomen was soft and bulging, and the bladder was readily palpable. There was a flaccid paraplegia of the lower extremities, but some slight tone in the lower abdominal muscles was present. There was anesthesia below T-2. Stimulation of the legs produced active withdrawal, but no voluntary movement was ever seen. Mental retardation was obvious.

Roentgenograms of the vertebral column were normal. She continued to have intermittent fever with temperatures ranging to 105° F. Temperature control was poor, and it was apparent that she fared better when not wrapped too tightly in clothes, though tests for sweating with starch and iodine showed a fairly normal reaction below the level of injury.

Follow-up. Physical and mental development was slow. She was a sickly youngster with many bouts of fever and penumonia. She died at 3 3/12 years of age.

DISCUSSION

Birth injuries usually occur at the cervicothoracic junction. The obstetrician is capable of exerting a great amount of force on the legs by traction during the delivery of the head and shoulders in a breech presentation. Crothers[3-4] and Ford[1] have pointed out that the spinal column in the infant is a different type of structure than it is in the adult. The infantile vertebral bodies are a series of elastic cartilages surrounded by inelastic connective tissue. It was shown in the autopsy specimen that this column can be stretched 2 inches and the cervical cord pulled down ¼ inch. In breech deliveries when traction is applied to the legs and the head is held tightly by uterine contraction, the entire column may be stretched to the point of rupture of the meninges and cord. Below, the cord is anchored firmly by the lumbar roots and above by the large cervical roots and medulla. Only in the thoracic area where the roots are relatively fine, thin structures is there little added support to the cord. The chance of injury is increased if lateral traction is also applied. Piper forceps are applied by many obstetricians to the aftercoming head to prevent traction on the neck.

In vertex deliveries where there has been damage to the cord there usually has been an arm extended over the head so that there was need for a great deal of lateral as well as direct traction. Injury here may occur between the head and C-1 in which case resultant damage might be fatal. A lesion at a lower level would produce signs similar to those following breech delivery.

Rupture of the dura mater and leptomeninges commonly is observed at autopsy. These membranes are frequently torn before damage to the cord occurs, since they act as a protective mechanism because of their greater strength. Rarely is there damage to the bony column and in none of our 6 cases was there evidence of fracture or dislocation.

The composite history of a child with this syndrome would usually be that of an infant born by a breech delivery. There are, however, well-documented case reports of these injuries following vertex presentation. In fact, 7 of Crothers'[25] 28 patients were born by vertex deliveries. The infant more than likely would be difficult to resuscitate and immediate paralysis of the lower extremities would be present. Some cases would also have accompanying brachial plexus injury. Neurological examination at a later date would indicate that the child was in no acute distress unless he was being treated for pneumonia, a frequent complication due to intercostal paralysis. The child would lie with his thighs partly flexed and abducted in the frog-leg position and would have a soft bulging abdomen. The cry would be weak but strengthened remarkably when abdominal compression was applied to aid in fixation of the muscles. Voluntary motor power of the legs would be absent. A sensory level to C-8 to T-1 is the usual finding though often the motor and sensory deficit is not appreciated since stimulation might produce reflex movement. The sensory level is tested most carefully by watching facial expression. No grimacing or crying occurs in spite of reflex movement until the upper limit of the sensory deficit is reached. One of the cases (Case 5) was unusual in that the level of the lesion was in the low thoracic area. Loss of sweating below the lesion is thought to account for some of the high fevers. These children have a poor temperature-regulating mechanism and the best way to reduce their fever is to lower the environmental temperature rather than by the usual therapy of aspirin and sponges of alcohol. Surprisingly, none of the 4 surviving children have these swings of fever. One (Case 4) has developed a sweating mechanism below the lesion which was absent previously as shown by the iodine test (for starch). The manner of recovery of sweating in a paraplegic is indefinite but has also been reported in adults with cord injuries; it presumably reflects an intact isolated sympathetic nervous system.[19] It was pointed out many years ago[19-20] that in either complete or partial cord lesions there might be independent reflex activity below the site of injury. This was dependent on an intact isolated segment. On autopsies of newborn infants with birth injuries focal damage in the low cervical area as well as secondary diffuse destruction of the cord is observed frequently.[1, 21, 22] Of our 6 patients, 5 had reflex activity. Twenty-three of Crothers' 28 patients also developed reflexes which would indicate that the majority of these lesions are focal in nature.

It would be expected that a complete block of the spinal fluid would occur because of the dense leptomeningeal adhesions. This, however, is not true invariably. Two myelograms were performed. In Case 1 (Fig. 1) the dye flowed readily to the high cervical area, although the site of disruption of the cord could be seen. There was a complete block in Case 3 (Fig. 2), and at operation dense adhesions of the meninges were found which could account for it.

DIFFERENTIAL DIAGNOSIS

The diagnosis of birth injuries of the spinal cord should not be difficult if the basic requirements are kept in mind, namely, a nonprogressive lesion usually following a difficult breech delivery. The single most important test is the demonstration of a sensory level. Amyotonia congenita (Oppenheim's disease) and infantile muscular atrophy (Werdnig-Hoffmann) are frequently mentioned in the differential diagnosis. Symptoms in these may be obvious at birth, but they are progressive diseases where the entire muscular system may be involved. There is usually excessive mobility of all joints; reflexes are diminished or absent but there is no sphincter disturbance as contrasted to an atonic anal sphincter associated with injuries of the cord. Sensation in diseases involving the anterior horn cells is normal. Lack of a sensory level should also rule out the atonic cerebral diplegias, cerebral palsy, and infantile muscular dystrophies. Tumors of the spinal cord and dermoids are described in infancy but other findings and their progressive nature should differentiate them.[23-28]

TREATMENT

Treatment is supportive. These children are prone to infections of the bladder because of urinary retention and to various pneumonic processes as a result of an impaired respiratory condition. Orthopedic procedures, bracing, and physiotherapy are necessary and important adjuncts. The extent of the fusion performed in Case 4 is an example of this. The value of laminectomy in acute transection of the cervical cord is debatable whether the injury occurs in an infant or in an adult. Children with injuries of the cord usually can attend school as they are not necessarily mentally retarded.

SUMMARY

The composite findings in 6 cases of birth injuries of the spinal cord have been presented with summaries of their subsequent courses. It is thought worth while to present this problem again since many clinicians are unaware of it. The patient who has paraplegia from birth with a demonstrable sensory level, respiratory distress, and a history of a difficult breech delivery should be suspected of having a birth injury of the spinal cord.

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Acid-base abnormalities in humans associated with the use of the Gibbon-Mayo pump

Flow rates of 2 to 24 liters per square meter of body surface per minute

Alexis F. Hartmann, Jr., M.D.,* Albert Roos, M.D., and David Goldring, M.D.

ST. LOUIS, MO.

IN OUR initial experience with patients who were operated upon with use of the Gibbon-Mayo pump, it was noted that approximately 4 hours postoperatively the status of some of the patients seemed very precarious, although the arterial oxygen saturation of blood drawn from the femoral artery was 80 to 90 per cent. The patients exhibited a pallid type of cyanosis and were hypotensive. Their peripheral arterial pulses were weak to absent and they showed either marked restlessness or depression. Femoral vein blood drawn during this period revealed oxygen saturations under 40 per cent and moderate acidemia. This acidemia has been described by Ito[1] in studies on animals and humans; he suggested that a diminished cardiac output might be the cause. He also advised the use of sodium bicarbonate in the postoperative period in an effort to correct this disturbance. Paneth[2] has studied the blood electrolyte changes in animals during extracorporeal support and has shown that the development of metabolic acidosis during bypass was inversely proportioned to the flow rate of the pump. Clowes[3] also showed that the postoperative acidosis was increased markedly in the animals that were progressing poorly and that subsequently died. Litwin[4] has studied the relationship between flow rate and the development of acidemia in humans; DeWall[5] demonstrated that there is a consistent moderate plasma bicarbonate depression during total body perfusion which is more pronounced in the cyanotic group of patients than in the acyanotic group. Since this problem is by no means explained or solved, it was decided to conduct studies which would help clarify it, i.e., time the onset of this large arteriovenous difference in blood oxygen saturation and acidemia and suggest an explanation for their development.

From the Departments of Physiology, Surgery, and Pediatrics, Washington University School of Medicine, St. Louis, Mo.

This work was supported by a grant from the St. Louis Heart Association and The Hartford Foundation.

**Address, Department of Pediatrics, St. Louis Children's Hospital, 500 South Kingshighway, St. Louis 10, Mo.*

METHODS

The venous blood of 22 patients (9 acyanotic, 13 cyanotic) was analyzed preoperatively for the following constituents: pH,*

*The pH determinations were made with the Beckman Model G pH Meter.

plasma CO_2* content from which the pCO_2 and the excess of acid were calculated,† plasma chloride, Na,‡ K,‡ NPN, Ca, P, and total and fractional proteins.

Prior to 29 operative procedures and after equilibration with 97 per cent air and 3 per cent CO_2 (gas flow, 10 L. per minute and blood temperature, 35 to 37° C.) blood samples were drawn from the pump and analyzed for the above constituents.

After 20 to 58 minutes of bypass with a flow rate of 2 to 2.4 L. per square meter of body surface area per minute (near the end of the operation), blood samples were drawn from the venous side of the pump and the above blood constituents were again determined.

In 9 patients, just prior to bypass, arterial blood samples were analyzed for pH and whole blood CO_2 content, and pCO_2 and the excess of acid were calculated.

The following studies were made on patients' blood 3 to 4 hours postoperatively: pH, whole blood CO_2 content, lactic acid,§ oxygen saturation‖ and calculated pCO_2, and excess of acid. Femoral vein blood samples were drawn from 18 patients and femoral artery samples from 7 patients who subsequently survived extracorporeal surgical procedures.

The above blood chemical constituents were determined for venous and arterial blood from patients who subsequently died after an extracorporeal surgical procedure (venous samples from 12 patients and arterial samples from 4).

The blood chemical findings in the above two groups were compared with the findings in 5 patients who underwent repair of congenital cardiac malformations under hypothermia and in 4 patients who had surgical correction of a patent ductus arteriosus.

*The CO_2 content of whole blood and plasma was determined by the method of VanSlyke and Neill.[6]

†The pCO_2 and calculated excess of acid were determined from the nomogram of Singer and Hastings.[7]

‡The sodium and potassium were determined with the Coleman flame photometer.

§Lactic acid was determined by the method of Barker and Summerson.[8]

‖Oxygen saturation was determined by the method of Roos and Rich.[9]

RESULTS

In an effort to learn when the changes (large arteriovenous differences and acidemia) observed in the postoperative period first made their appearance, it was decided to study the patients preoperatively. The blood samples upon which the determinations were made, as summarized in Table I, were drawn 24 hours before operation from an antecubital vein with use of a tourniquet. The patients were divided into cyanotic and acyanotic groups. The blood chemical constituents were essentially within normal limits for both groups. The slight tendency toward acidemia in both groups may have been produced by the method which was used to obtain the blood samples.

It was next decided to study the donors' blood for any unusual chemical changes. Blood samples were drawn from the pump before 29 operative procedures for analysis of chemical constituents, as shown in Table II. Each sample of blood represented a mixture of blood from 9 donors. The donors were bled 2 to 2½ hours prior to the sampling and the blood was not refrigerated. The pump was primed and the blood circulated continually for 30 minutes through the lung portion of the pump. A mixture of 97 per cent air and 3 per cent CO_2 was passed through the lung at 10 L. per minute. The temperature of the blood was maintained between 34° and 37° C. by an external heating apparatus. The samples of blood were drawn just before the patient was placed upon bypass.

The plasma CO_2 content was slightly low (average of 19.4 mEq. per liter), but the pH was at the lower limits of normal (average pH of 7.35). This indicates a mild metabolic acidosis (acid excess 4.4 mEq. per liter) which was completely compensated by the aeration achieved by the mechanical lung (average pCO_2, 34.3 mm. Hg). This metabolic acidosis was caused by lactic acid produced by glycolysis (average of 4.1 mEq. per liter of lactic acid)

Table I. Preoperative findings

*Diagnosis**	*pH*	*Plasma CO_2 content (mEq./L.)*	*pCO_2 (mm. Hg)*	*Calculated excess of acid (mEq./L.)*	*Na (mEq./L.)*
Acyanotic					
Interatrial septum secundum defect (1)		23.8			140
Interventricular septal defect (4)	7.33	27.5	50	0	144
Interventricular septal defect (5)		24.8			146
Tetralogy of Fallot		30.2			135
Interventricular septal defect (6)	7.40	27.2	43	0	143.5
Interventricular septal defect (7)	7.36	24.9	43	0	140
Tetralogy of Fallot	7.36	26.1	45	0	142
Interatrial septum secundum defect	7.28	29.0	59	0	
Interventricular septal defect	7.34	29.8	53	0	144
Average	7.34	27.0	49	0	142.5
Cyanotic					
Tetralogy of Fallot (2)		23.0			143
Interatrial septum secundum defect plus pulmonary valvar stenosis (3)	7.30	22.6	43.5	2	146
Tetralogy of Fallot (8)	7.30	22.0	42.5	3	129
Tetralogy of Fallot		22.8			133
Tetralogy of Fallot		24.4			140
Tetralogy of Fallot		21.4			148
Interatrial septum secundum defect plus pulmonary valvar stenosis	7.35	26.3	46	0	148
Complete anomalous venous drainage	7.32	25.0	46	0	148
Tetralogy of Fallot		24.3			126
Tetralogy of Fallot	7.36	23.2	39.5	1	144
Tetralogy of Fallot	7.21	23.0	53	3	145
Interventricular septal defect, pulmonary atresia plus patent ductus arteriosus	7.31	24.1	46	0	140
Interatrial septum secundum defect, pulmonary atresia plus patent ductus arteriosus	7.38	24.0	39	0	137
Average	7.32	23.5	44.4	1.1	140

*The numbers next to the diagnostic labels identify the patients from whom blood samples were obtained for study preoperatively, at the end of bypass, and postoperatively.

since the blood was not refrigerated and was not placed in the pump for 2 to 2½ hours. The blood in the pump was also diluted approximately 6 per cent by mixture with physiologic saline solution (30 c.c. of isotonic saline solution was present in each unit of donor blood). During the screening of the lung with blood, small additional amounts of isotonic saline solution were added also. This dilution of the blood, therefore, further lowered the final value of the plasma CO_2 content. All of the other blood constituents were within normal limits except for a slight lowering of the plasma inorganic phosphorus level which cannot be explained.

Although the effects of anesthesia and thoracotomy have been well studied by Gabbard[10] and Beecher,[11] it was decided, nevertheless, to see what changes occurred in the arterial blood of the patients. Arterial blood samples were drawn from the femoral or brachial artery in 9 patients under general endotracheal anesthesia* with the chest open and while respiration was assisted mechanically. These blood samples were drawn just prior to bypass. As shown in Table III, the blood constituents show a mild compensated type of metabolic acidosis.

*All patients received Pentothal Sodium nitrous oxide and oxygen, and muscle relaxants.

K (mEq./L.)	*Ca* (mg. %)	*Cl* (mEq./L.)	*Total protein* (Gm. %)	*Albumin* (Gm. %)	*Globulin* (Gm. %)	*Inorganic phosphorous* (mg. %)	*N.P.N.* (mg. %)
4.0		102.0					23.3
4.7	12.0	106.0	6.00	4.35	1.65	4.7	29.0
4.3		101.0					27.0
4.0		92.5					45.9
4.0		95.0					
4.7		99.0					27.2
4.7	10.6	106.0	6.15	3.93	2.22	6.0	37.5
	10.4	100.0	6.50	4.15	2.35	5.5	36.0
4.6	12.0	101.0	7.05	4.13	2.92	6.0	24.5
4.6	11.2	100.3	6.43	4.14	2.28	5.6	31.3
3.9	12.0	104.0				4.9	27.8
4.4	12.2	100.0				5.1	28.0
4.2	11.2	102.0					26.0
4.6	11.8	95.0				4.1	27.6
5.3		104.0					36.8
4.6	12.8	97.0				5.3	39.0
4.5		100.0					36.5
4.9	11.2	104.0				4.3	29.0
4.0	9.6	97.0	6.15	4.46	1.69	4.8	30.0
3.2	11.0	98.5				4.1	35.7
4.1	11.0	106.0	6.50	4.65	1.85	4.6	26.2
4.0	9.4	109.0	7.35	3.55	3.80	5.8	50.0
3.2	10.2	104.0	7.83	5.30	2.53	5.5	38.5
4.8	11.1	101.5	6.96	4.49	2.47	4.8	33.2

It was important to find if any marked aberrations of the blood chemical constituents occurred during extracorporeal support, so after an average time of 39 minutes on bypass, with flow rates of 2 to 2.4 L. per square meter of body surface area per minute, venous blood samples were withdrawn for analysis. The results are summarized in Table IV. The acid excess after bypass is definitely less (average of 1.7 mEq. per liter) than before bypass (average of 4.1 mEq. per liter) as shown in Table III. The pCO_2 is higher at this time (average pCO_2, 45.8 mm. Hg) than before bypass (average, 34.3 mm. Hg) because the patient is constantly adding CO_2 to the system. The metabolic acidosis is, therefore, less well compensated during bypass than before, and the pH is slightly lower (average of 7.30). The original gas mixture (97 per cent air and 3 per cent CO_2) going through the mechanical lung was changed to 100 per cent oxygen (10 L. per minute) during the period of bypass. The arterial blood oxygen saturation was 96.5 per cent (average), which indicates excellent oxygenation of the blood by the mechanical lung. The venous blood oxygen saturation was 67.9 per cent (average). The blood oxygen saturation, the arteriovenous difference, and the diminished metabolic acidosis during bypass indicate an adequate blood flow rate

Table II. Pump before bypass

Diagnosis	*pH*	*Plasma CO_2 content*	*pCO_2 (mm. Hg)*	*Calculated excess of acid*	*Lactic acid (mEq./l.)*
Interventricular septal defect	7.42	20.8	31.5	2	5.3
Tetralogy of Fallot	7.33	19.8	36	4	4.4
Interventricular septal defect, patent ductus arteriosis, plus coarctation of aorta	7.31	18.3	35	6	5.6
Interventricular septal defect	7.30	20.8	40	3	4.2
Interventricular septal defect	7.38	20.0	32.5	3	4.2
Interventricular septal defect	7.38	18.6	30.5	5	4.1
Tetralogy of Fallot	7.33	18.8	34	5	3.9
Interventricular septal defect	7.35	18.4	33	5	4.8
Interventricular septal defect	7.38	17.8	29.5	6	4.8
Rheumatic heart disease and aortic stenosis	7.30	19.6	38	5	5.0
Interventricular septal defect	7.28	23.2	47	2	4.0
Ostium primum defect	7.28	18.5	38	6	4.9
Tetralogy of Fallot	7.34	20.2	36	4	3.4
Interventricular septal defect	7.31	18.2	34.5	6	3.1
Rheumatic heart disease and mitral insufficiency	7.30	20.2	39	4	4.4
Interatrial septum secundum defect	7.30	21.4	41.5	3	2.8
Tetralogy of Fallot	7.30	19.7	38	5	3.2
Interatrial septum secundum defect plus pulmonary valvular stenosis	7.42	19.3	29	4	3.7
Tetralogy of Fallot	7.30	19.8	38	5	3.1
Interventricular septal defect	7.33	19.0	34.5	5	3.6
Interventricular septal defect	7.40	20.2	31.5	3	3.2
Ostium primum defect	7.38	21.0	34	3	2.8
Tetralogy of Fallot	7.30	20.4	40	4	4.8
Tetralogy of Fallot	7.40	15.8	25	7	4.0
Interventricular septal defect	7.41	18.8	29	4	4.1
Interventricular septal defect	7.34	19.5	35	4	3.6
Tetralogy of Fallot	7.43	19.0	28	4	3.4
Rheumatic heart disease and mitral insufficiency	7.40	17.8	28	5	5.6
Interventricular septal defect	7.38	16.9	28	7	4.3
Average	7.35	19.4	34.3	4.4	4.1

for the patients' metabolic needs during this period. The other blood chemical determinations were within normal limits.

It was quite certain, therefore, that the blood chemical changes (large arteriovenous differences and acidemia) occur in the immediate postoperative period, and this was shown by the next study. Three to 4 hours postoperatively, venous and arterial blood samples were obtained from the femoral vessels for study of patients who were operated upon with the aid of the pump. The patients are divided into 2 groups: the survivors (Table V) and the nonsurvivors (Table VI). There are marked arteriovenous differences in the pH, whole blood CO_2, pCO_2, and blood oxygen saturation of the survivors (Table V)*; these are even more marked in the group of patients in Table VI. Approximately 10 patients who subsequently died are not included in this group since it was impossible to obtain blood samples from them because of their critical state. It is certain that the blood chemical values in the nonsurvivor group would have shown even greater arteriovenous differences if all patients had been included.

Finally, it was felt that it would be of interest (and would also provide controls) to see what the postoperative blood chemical changes were in patients who under-

*As will be noted, arterial samples could not be obtained from all patients in this group because of technical difficulties. This was also true for the patients listed in Table VI.

Na (mEq./L.)	*K (mEq./L.)*	*Ca (mg. %)*	*Cl (mEq./L.)*	*Total protein (Gm. %)*	*Albumin (Gm. %)*	*Globulin (Gm. %)*	*Inorganic phosphorous (mg. %)*	*Oxygen saturation (%)*
144	3.1	8.9	105	4.50	3.06	1.44	2.3	99.1
145	3.3	10.4	104	6.35	4.25	2.37	2.6	99.3
146	3.3	9.9	104	6.00	4.36	1.64	2.8	97.9
145	3.0	10.6	104	6.15	4.57	1.58	3.0	96.2
145	3.5	9.3	104	5.88	4.19	1.66	2.2	96.8
146	3.3	9.9	106	6.09	4.25	1.84	2.4	92.3
144	3.1	10.8	101	6.50	4.50	2.00	2.5	100.6
144	3.6	11.3	100	6.66	4.90	1.76	2.7	98.7
150	3.2	10.9	99	6.35	4.50	1.85	2.2	98.7
139	3.2	9.8	110	5.25	3.36	1.89	3.5	97.4
140	3.4	9.6	109	5.40	3.53	1.97	2.7	98.1
145	2.8	9.9	106	6.15	4.64	1.51	2.4	96.8
140	3.2	10.7	101	5.90	4.15	1.75	2.2	93.1
141	3.0	10.6	103	6.15	4.77	1.38	2.5	94.7
140	3.4	10.4	108	5.40	3.38	2.02	2.4	99.3
145	3.4	10.0	105	6.15	4.40	1.75	2.3	96.7
139	3.3	10.4	98	6.24	4.90	1.34	2.5	93.7
140	3.8	10.0	96	6.35	4.25	2.10	2.5	94.7
145	3.3	10.0	98	6.50	4.63	1.87	3.2	98.7
144	3.0	11.0	100	5.95	4.25	1.70	2.5	96.5
145	3.5	10.4	103	5.45	3.45	2.00	2.3	98.2
144	3.6	10.0	107	5.30	3.26	2.04	3.7	94.4
140	3.6	10.2	97	6.32	4.45	1.87	4.5	96.5
145	3.8	11.0	102	7.45	4.16	3.29	3.9	96.9
144	3.6	9.8	102	5.70	4.15	1.55	2.4	94.7
139	3.5	9.0	100	5.43	3.38	2.05	2.6	99.5
139	3.2	11.4	105	7.44	4.57	2.87	3.0	98.0
140	3.5	10.0	106	5.45	3.64	1.81	2.2	94.8
145	3.7	9.6	100	6.50	4.76	1.74	3.9	95.0
143	3.35	10.2	103	6.03	4.16	1.88	2.76	96.8

Table III. Patients before bypass

Diagnosis	*pH*	*Whole blood CO_2 content (mEq./L.)*	*pCO_2 (mm. Hg)*	*Calculated excess of acid (mEq./L.)*
Interventricular septal defect	7.45	16.0	27.0	2
Tetralogy of Fallot	7.48	17.7	29.5	0
Interventricular septal defect	7.42	19.7	34.0	1
Tetralogy of Fallot	7.42	14.9	27.0	4
Interventricular septal defect, patent ductus arteriosus, and coarctation of aorta	7.38	15.3	32.0	2
Interventricular septal defect	7.22	17.4	49.0	6
Interatrial septum secundum defect and pulmonic stenosis	7.40	15.5	31.0	2
Interventricular septal defect	7.32	14.8	32.5	6
Tetralogy of Fallot	7.25	14.0	37.0	8
Average	7.37	16.1	33.2	3.4

Table IV. Venous side of pump during bypass

*Diagnosis**	*pH*	*Plasma CO_2 content (mEq./L.)*	*pCO_2 (mm. Hg)*	*Calculated excess of acid (mEq./L.)*	*Lactic acid (mEq./L.)*	*Na (mEq./L.)*
Interventricular septal defect	7.48	19.6	26.0	3	6.1	140.5
Tetralogy of Fallot	7.40	21.0	33.0	2	3.8	142
Interventricular septal defect	7.37	18.3	30.5	5	5.6	142
Interventricular septal defect	7.20	27.0	66.0	0	3.2	145
Interventricular septal defect	7.30	24.9	48.0	0	2.4	144
Tetralogy of Fallot	7.20	18.3	44.0	7	6.3	141
Interventricular septal defect	7.32	18.9	35.0	5	6.0	146
Interventricular septal defect	7.28	24.6	50.0	0	3.6	145
Rheumatic heart disease and aortic stenosis	7.31	28.0	52.5	0	2.5	143
Interventricular septal defect	7.22	25.8	59.0	0	2.4	133
Ostium primum defect	7.16	24.6	65.0	1	3.3	138
Tetralogy of Fallot	7.30	25.2	49.0	0	2.6	135
Interventricular septal defect	7.28	22.7	46.0	2	1.9	141
Rheumatic heart disease and mitral insufficiency	7.21	26.2	62.0	0	3.2	137
Interatrial septum secundum defect (1)	7.18	23.4	59.0	2	6.0	143
Tetralogy of Fallot (2)	7.31	22.8	43.0	1	2.8	137
Interatrial septum secundum defect plus pulmonic stenosis (3)	7.22	24.2	55.5	1	3.7	140
Tetralogy of Fallot (8)	7.30	22.2	43.0	2	2.5	145
Interventricular septal defect (4)	7.24	24.0	53.0	1	3.1	143.5
Interventricular septal defect	7.39	25.6	41.0	0	2.6	140
Ostium primum defect	7.29	22.4	45.0	2	2.4	142
Tetralogy of Fallot	7.35	20.6	36.0	3	4.1	140
Tetralogy of Fallot	7.30	22.1	43.0	2	3.2	138
Interventricular septal defect (5)	7.40	21.4	32.0	3	4.1	144
Interventricular septal defect	7.31	24.7	47.0	0	4.0	139
Tetralogy of Fallot	7.27	19.6	40.0	5	3.4	135
Interventricular septal defect (6)	7.42	22.5	33.5	0.5	5.0	144
Interventricular septal defect (7)	7.30	22.9	44.0	1	4.1	143
Average	7.30	23.0	45.8	1.7	3.7	141

*The numbers next to the diagnostic labels identify the patients from whom blood samples were obtained for study preoperatively, at the end of the bypass, and postoperatively.

went hypothermic procedures and also in patients who had undergone a unilateral thoracotomy. The arteriovenous differences were, therefore, determined 3 to 4 hours postoperatively in 4 patients who had successful repair of an interatrial septum secundum defect (2 patients) and pulmonic valvar stenosis (2 patients). The repair was carried out under hypothermia with outflow and inflow occlusion of 3 to 4 minutes. As shown in Table VII, the arteriovenous differences are small and much less than in the previous two groups of patients (Tables V and VI). Similar studies were also performed on 4 patients who had repair of a patent ductus arteriosus (Table VIII), and it is not surprising to find that the arteriovenous differences were also small in them.

DISCUSSION

These studies indicate that the large arteriovenous differences and metabolic acidosis appear postoperatively, since there is less metabolic acidosis in the blood while the patient is on bypass than was present even in the donor blood prior to bypass. It is felt that these large arteriovenous differences and the clinical appearances of the patients are reflections of poor circulation. This could be accounted for by: (1) low cardiac output, (2) local vasospasm, or (3) a combination of both.

K (mEq./L.)	Ca (mg. %)	Cl (mEq./L.)	Total protein (Gm. %)	Albumin (Gm. %)	Globulin (Gm. %)	Inorganic phosphorous (mg. %)	Oxygen saturation (%)		Time on bypass (Minutes)
							Venous	Arterial	
3.4	9.1	101	4.70	3.26	1.44	3.9	77.5	97.3	40
4.3	11.4	99	6.08	3.03	2.05	4.4	62.7	95.7	47
3.1	11.4	102	6.19	4.50	1.69	4.4	82.8	95.6	38
4.2	11.9	102	6.33	3.93	2.40	4.5	66.1	98.7	53
4.0		100	5.87	4.00	1.87	3.8	70.6	96.9	27
3.2	11.4	99	7.02	5.02	2.00	6.1	75.0	98.7	40
3.7	10.6	102	6.00	4.90	1.10	4.1	65.5	95.7	21
4.4	12.5	95	7.04	5.02	2.02	3.6	75.4	99.7	50
4.3	9.9	100	5.60	3.46	2.14	3.7	63.8	97.8	22
3.2	10.7	104	5.40	3.31	2.09	2.7	60.3	99.1	27
3.4	9.4	100	6.49	4.77	1.72	3.9	67.2	97.3	33
4.7	10.7	96	6.25	4.25	2.00	3.9	74.4	96.1	35
3.1	11.9	99	6.15	4.50	1.65	3.1	63.3	93.2	40
3.4	10.0	96	6.15	3.60	2.55	2.9	68.8	97.8	36
3.0	11.6	102	6.50	4.40	1.75	3.1	80.2	97.5	48
4.4	11.3	101	6.07	4.77	1.30	3.9	61.0	95.6	35
4.0	10.6	97	6.10	4.03	2.07	4.2	54.5	95.5	25
3.9	10.6	96	6.56	4.26	2.30	4.7	52.3	99.5	35
3.0	11.6	100	5.85	3.87	1.98	3.4	69.1	97.0	43
4.0	11.0	99	5.85	3.64	2.21	2.2	77.2	96.5	53
4.2	10.0	94	6.00	3.50	2.50	2.4	73.4	96.6	35
4.8	10.4	99	7.05	4.15	2.90	4.6	66.5	95.9	58
5.1	10.4	99	7.65	4.64	3.01	2.0	67.0	96.7	43
4.0	10.4	97	6.50	4.10	2.40	3.0	66.3	93.6	33
3.3	10.4	97	5.40	3.74	1.66	2.6	68.0	96.0	33
4.6	11.4	101	6.49	4.90	1.59	4.3	63.0	100.0	47
2.9	10.4	100	5.85	3.59	2.26	3.6	72.4	93.4	
4.2	9.0	104	6.50	4.64	1.86	2.7	57.9	94.0	20
3.85	10.7	99	6.20	4.14	2.02	3.6	67.9	96.5	39

Work is presently in progress to study directly the cardiac output in this postoperative state which we feel will shed light on this problem.

A number of factors may be cited which might explain the postoperative status of these patients. These are: (1) nature of the congenital cardiac malformation, status of the patient's myocardium, and pulmonary vascular resistance prior to operation; (2) surgical trauma, i.e., ventriculotomy necessary for exposure of the defect and complete heart block subsequent to the repair; (3) duration of cardiac arrest; (4) blood volume of patient at the end of the operative procedure; and (5) length of time of extracorporeal support. Studies are being initiated to attempt to evaluate the relative importance of these factors.

SUMMARY

1. With use of a Gibbon-Mayo pump with a flow rate of 2 to 2.4 L. per square meter of body surface area per minute and after an average time of 39 minutes of bypass, less metabolic acidosis was found to be present in the blood than was present in the donor blood prior to bypass. The blood oxygen arteriovenous differences are acceptable (artery, 96 per cent; vein, 67 per cent).

2. The poor clinical status, metabolic

Table V. Survivors (3 to 4 hours postoperation)

*Diagnosis**	*pH*	*Whole blood CO_2 content (mEq./L.)*	*pCO_2 (mm. Hg)*	*Calculated excess of acid (mEq./L.)*	*Lactic acid (mEq./L.)*	*Oxygen saturation (%)*
Arterial blood						
Interventricular septal defect (4)	7.30	20.2	45	2		
Interventricular septal defect (6)	7.22	20.2	52	3	3.1	89.2
Tetralogy of Fallot	7.34	16.9	35	4	5.4	91.9
Tetralogy of Fallot	7.26	18.4	45	4	2.6	87.3
Interatrial septum secundum defect	7.31	17.1	38	4	3.7	100.0
Tetralogy of Fallot	7.32	16.7†	31.5	7	5.2	90.9
Interatrial septum secundum defect	7.32	18.1	40	3	2.6	92.5
Interventricular septal defect	7.28	16.1	40	5	3.5	84.5
Average	7.29	18.1	40.8	4	3.7	90.9
Venous blood						
Interventricular septal defect	7.29	22.3	53	0	3.9	
Tetralogy of Fallot	7.13	20.6	66	6	6.2	
Tetralogy of Fallot	7.30	19.5	44	2.5		
Tetralogy of Fallot	7.15	26.5	80	0		
Interventricular septal defect	7.22	21.5	57	3		
Interatrial septum secundum defect (1)	7.10	20.2	70	7		
Tetralogy of Fallot (2)	7.25	20.5	52	3		
Interatrial septum secundum defect plus pulmonic stenosis (3)	7.21	22.7	60	3		
Interventricular septal defect (4)	7.20	21.8	61	3		
Interventricular septal defect (5)	7.19	22.7	63	3	5.6	
Interventricular septal defect (6)	7.14	23.8	72	3		22.2
Interatrial septum secundum defect plus pulmonic stenosis	7.38	24.4	44	0	4.2	39.3
Interventricular septal defect (7)	7.20	25.6	71	0	3.8	31.2
Tetralogy of Fallot	7.22	21.5	57	3	5.8	28.0
Tetralogy of Fallot	7.20	22.2	62	3	2.6	31.4
Interatrial septum secundum defect	7.20	19.5	54	5	4.5	73.0
Tetralogy of Fallot	7.10	20.3	70	7	7.6	0.0‡
Interatrial septum secundum defect	7.22	22.1	61	3	3.4	53.6
Interventricular septal defect	7.18	20.7	60	5	5.1	0.0‡
Average	7.20	22.0	60.9	3.1	4.8	31.0

*The numbers next to the diagnostic labels identify the patients from whom blood samples were obtained for study preoperatively, at the end of bypass, and postoperatively.

†Plasma CO_2 content omitted from average.

‡This value for the oxygen saturation by this method means 0 to 10 per cent.

Table VI. Nonsurvivors (3 to 4 hours postoperation)

Diagnosis	*pH*	*Whole blood CO_2 content (mEq./L.)*	*pCO_2 (mm. Hg)*	*Calculated excess of acid (mEq./L.)*	*Lactic acid (mEq./L.)*	*Oxygen saturation (%)*
Arterial blood						
Tetralogy of Fallot	7.24	13.9	36	9	7.3	88.5
Interventricular septal defect, pulmonary atresia, plus patent ductus arteriosus	7.30	17.6	40	4	4.1	89.2
Interventricular septal defect plus aortic insufficiency	7.29	17.6	39	4	4.4	87.6
Interventricular septal defect	7.32	19.6	43	2	5.1	58.2
Average	7.29	17.2	39.5	4.8	5.2	80.8

Table VI. *continued*

Diagnosis	pH	Whole blood CO_2 content (mEq./L.)	pCO_2 (mm. Hg)	Calculated excess of acid (mEq./L.)	Lactic acid (mEq./L.)	Oxygen saturation (%)
Venous blood						
Interventricular septal defect	7.15	20.9	63	5		
Tetralogy of Fallot	7.12	14.6	47	12	10.4	
Ostium primum defect	7.13	23.3	74	4		
Ostium primum defect	7.22	22.2	60	2		
Tetralogy of Fallot (8)*	6.88	15.2	80	19		
Tetralogy of Fallot	7.18	23.9	67	2	5.8	
Tetralogy of Fallot	7.10	18.6	62	9	8.9	34
Interventricular septal defect, pulmonary atresia, plus patent ductus arteriosus	7.20	20.9	58	4	5.0	15.8
Interatrial septum secundum defect, plus pulmonary atresia, plus patent ductus arteriosus	7.20	20.3	57	5	3.8	29.8
Interventricular septal defect plus aortic insufficiency	7.18	21.5	56.5	5	5.6	5.8
Interventricular septal defect	7.22	19.6	50.5	4	6.6	0.0†
Tetralogy of Fallot	7.19	18.8	53	6	5.1	12.3
Average	7.15	20.0	60.7	6.4	6.4	16.3

*The number next to the diagnostic label identifies the patient from whom blood samples were obtained for study preoperatively, at the end of bypass, and postoperatively.

†This value for the oxygen saturation by this method means 0 to 10 per cent.

Table VII. Hypothermia (3 to 4 hours postoperation)

Diagnosis	pH	Whole blood CO_2 content (mEq./L.)	pCO_2 (mm. Hg)	Calculated excess of acid (mEq./L.)	Lactic acid (mEq./L.)	Oxygen saturation (%)
Arterial blood						
Pulmonic stenosis	7.40	19.7	35	0	3.5	89
Pulmonic stenosis	7.32	26.8*	54	0	2.9	95
Average	7.36		43.2	0	3.2	92
Venous blood						
Interatrial septum secundum defect	7.20	21.8	61	3	6.4	58
Pulmonic stenosis	7.22	22.8	61	2	4.1	
Interatrial septum secundum defect	7.28	18.1	43	4	6.3	79
Pulmonic stenosis	7.28	31.0*	63	0	3.7	60
Average	7.25	20.9	57	2.2	5.1	66

*Plasma CO_2 content omitted from average.

acidosis, and marked arteriovenous differences in pH, CO_2, pCO_2, and oxygen saturation observed in some of the patients develop postoperatively and are probably due to poor cardiac output or vasospasm or a combination of both. Possible causes for this state have been enumerated.

3. Studies are in progress to evaluate directly the cardiac output of these patients in the postoperative state.

Table VIII. Patients operated upon for patent ductus arteriosus (3 to 4 hours postoperation)

Diagnosis	*pH*	*Whole blood CO_2 content (mEq./L.)*	*pCO_2 (mm. Hg)*	*Calculated excess of acid (mEq./L.)*	*Lactic acid (mEq./L.)*	*Oxygen saturation (%)*
Arterial blood						
Patent ductus arteriosus	7.40	18.3	34	1	2.9	92
Patent ductus arteriosus	7.33	19.8	40	2	3.0	95
Patent ductus arteriosus	7.31	17.8	40	3	3.2	90
Patent ductus arteriosus	7.31	23.7*	45	0	2.0	95
Average	7.34	18.6	40	1.75	2.8	93
Venous blood						
Patent ductus arteriosus	7.32	19.6	43	2	2.9	84
Patent ductus arteriosus	7.33	20.8	45	1	3.0	83
Patent ductus arteriosus	7.30	18.7	42	3	3.2	77
Patent ductus arteriosus	7.28	24.5*	47	2	2.4	75
Average	7.31	19.7	44	2	2.9	80

*Plasma CO_2 content omitted from average.

We wish to express our thanks for the technical assistance of Miss Marge Hause, Mrs. Gwendolyn Goetz, Miss Marie Morton, and Mrs. Mary Hasler.

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Observations on rheumatic nodules over a 30-year period

Janet S. Baldwin, M.D.,† Josephine M. Kerr, M.D.,*

Ann G. Kuttner, M.D.,** and Eugenie F. Doyle, M.D.

NEW YORK, N. Y.

NODULES have been recognized as a characteristic manifestation of rheumatic fever for more than 100 years. In the opinion of most of the early observers, nodules were associated with an extremely bad prognosis.[1-8] Subsequently, more extensive studies based on larger numbers of cases showed that, although the mortality rate was high, the prognosis of patients with nodules was not uniformly bad.[9-12]

At the present time many observers have the impression that during the past 25 years both the incidence and the severity of rheumatic fever have declined. Since it is agreed generally that nodules usually are associated with a severe form of rheumatic fever, it was thought that a review of the immediate and long-term prognosis of patients with nodules observed during a 30-year period, 1928 to 1958, would serve as an indicator of changes in the pattern of this disease. In this paper the findings obtained during the first half of the 30-year period, 1928 through 1942, and the second half, 1943 to 1958, are compared.

From The Children's Cardiac Service, New York University-Bellevue Medical Center.

†*Deceased.*

**New York Heart Association Fellow. Present address, Department of Pediatrics, Albert Einstein College of Medicine, Bronx, N. Y.*

***Supported by funds donated by Public Health Service Grant (H-1540). Address, Department of Pediatrics, New York University College of Medicine, 550 First Avenue, New York 16, N. Y.*

PLAN OF STUDY

All the patients were hospitalized on the wards of the Children's Medical Service, Bellevue Hospital. At the time of discharge, the charts of every patient with rheumatic fever, both those with and those without nodules, were reviewed and summarized by a member of the Cardiac Attending Staff. After discharge these patients were followed at regular intervals in the Children's and Adolescent Cardiac Clinics by the same attending staff which had supervised their treatment during their hospital stay. Every patient with nodules admitted during the 30-year period, 1928 to 1958, was included in the study. The first half of this period, 1928 through 1942, is designated as Period A and the second half, 1943 to 1958, as Period B.

During the last 8 years of Period B, from 1950 to 1958, patients with rheumatic fever received on admission intramuscular injections of penicillin in doses sufficient to maintain therapeutic levels for 10 days in

Table I. Severity of carditis in patients with nodules

Carditis	*No. of episodes*	*% of total episodes (101)*
Severe	45	44.5
Moderate	39	38.6
Mild	17	16.8

order to eliminate any possible foci of group A streptococci. Thereafter, daily prophylactic doses of oral penicillin or sulfadiazine were given to prevent new infections with streptococci while the patients were on the ward. The same daily medication was continued after discharge. Adherence to the prophylactic regimen was checked during visits to the clinic every 2 to 3 months.

RESULTS

Clinical material. During the 30-year period from 1928 to 1958, 101 separate rheumatic episodes of carditis accompanied by nodules which occurred in 96 patients were analyzed. Five of these patients were admitted twice for separate attacks. During the first half of this period, 1928 through 1942 (Period A), 599 episodes of carditis associated in 68 instances with nodules were observed (11.4 per cent). During the second half, 1943 to 1958 (Period B), 349 attacks of carditis, accompanied in 33 instances by nodules, occurred (9.4 per cent).

Age. Nodules occurred in patients ranging in age from 3 to 13 years, with the highest incidence between ages 7 and 9. In children 3 to 6 years of age, nodules were observed in 14 patients, 7 boys and 7 girls, during Period A and in only 2 patients, both boys, during Period B.

Cardiac involvement. Definite evidence of concurrent active carditis was present in all of the 101 episodes. With a single exception, signs of active carditis were obvious prior to the appearance of nodules. In this 1 patient, clear-cut evidence of mild carditis developed 2 days after the nodules first were observed.

Severity of carditis. As shown in Table I, nodules were most common in patients with severe carditis. Carditis was classified as severe if signs of pericarditis, congestive failure, or rapidly increasing cardiac enlargement were present. In the 101 episodes, pericarditis was observed in 31 instances (30.7 per cent) and congestive failure in 45 instances (44.5 per cent). A diagnosis of moderate carditis was made when slight to moderate cardiac enlargement was accompanied by 3 or more of the following: heart sounds of poor quality, gallop rhythm, arrhythmia, tachycardia disproportionate to temperature, and new or changing cardiac murmurs. Mild carditis was considered to be present if similar signs were present but no or only questionable cardiac enlargement was demonstrable.

Other rheumatic manifestations were observed in patients with nodules. The incidences of these manifestations per 101 episodes were polyarthritis, 30; muscle and joint pain, 41; chorea, 9; erythema marginatum, 25; rheumatic pneumonitis, 8; erythema nodosum, 2; and abdominal pain, 29.

During the period that nodules were present, epistaxis occurred frequently. During Period A the episodes of epistaxis were often of such severity as to require transfusion for the correction of the anemia.

Characteristics of nodules. As noted by previous observers, nodules rarely develop early in the course of the attack at the time when the temperature is elevated markedly. They usually appear several weeks or even months after the onset of the attack and are most common in patients in whom signs of activity of the rheumatic process continue for several weeks or months. In many instances the exact length of time that the nodules persisted was not recorded accurately. The minimum period noted was 5 days and the maximum was 6 months. In the majority of cases, major and minor signs of active carditis persisted throughout the period that nodules were present. In many the severity of the carditis tended to diminish as the nodules regressed.

Prognostic significance of nodules. In our cases (Table II) the number of nodules was not correlated directly with the severity of the rheumatic attack. In 21 instances of severe carditis less than 10 nodules were

Table II. Severity of carditis as related to number of nodules

No. of nodules	*No. of episodes*	*Degree of carditis*			*Deaths during episode of nodules*
		Mild	*Moderate*	*Severe*	
Few (0 to 10)	46	13	12	21	10
Moderate (11 to 30)	41	3	22	16	5
Many (over 30)	10		4	6	3
Not given	4	1	1	2	
Total	101	17	39	45	18

Table III. Attacks of carditis, with and without nodules, and deaths within 9 months or less from the onset of the attack in the 2 periods

	*Total No. of attacks of carditis**	*No. of deaths*	*%*	*Carditis with nodules*	*No. of deaths*	*%*	*Carditis without nodules*	*No. of deaths*	*%*
Period A	599	98	16.4	68	15	22	531	83	15.6
Period B	349	15	4.3	33	3	9.1	316	12	2.8

*The table is based on the number of attacks of carditis and does not represent individuals. Some patients had more than one attack.

noted. Yet in the 46 rheumatic episodes with this small number of nodules, 10 deaths occurred. On the other hand, in 41 episodes associated with 10 to 30 nodules only 5 patients died. In only 10 episodes did the number of nodules exceed 30.

Incidence of carditis during the 30-year period. All cases of carditis, both those with and those without nodules, during the 30-year period were analyzed. During the first half of this period, 1928 through 1942 (Period A), the mortality rate was 16.4 per cent. During the second half, 1943 to 1958 (Period B), the mortality rate decreased to 4.3 per cent. The percentage of attacks of carditis associated with nodules during the two periods, however, remained approximately the same; attacks occurred in 68 of 599 episodes during Period A (11.3 per cent) and in 33 of 349 episodes during Period B (9.4 per cent). During Period B the mortality rate of patients with carditis associated with nodules did not fall as markedly as that of patients with carditis without nodules. This suggests that nodules should still be considered a sign of a *severe* rheumatic infection and that a guarded prognosis be given to individuals with this manifestation.

Deaths occurring within 9 months or less from the onset of attack. During the 101 rheumatic episodes accompanied by nodules, 18 patients (17.8 per cent) died from progressive carditis and congestive failure. Period A (1928 through 1942) differed strikingly from Period B (1943 to 1958). Period A included 68 episodes with 15 deaths (22 per cent) whereas during Period B there were 33 episodes with 3 deaths (9.1 per cent). Seven of these 18 patients died within 1 month, 7 within 4 months, and 4 within 5 to 9 months from the onset of the fetal rheumatic attack. The interval between the first appearance of nodules and death varied from 3 days to 7 months.

Recurrent crops of nodules. In accord with previous observations, it was found that recurrent crops of nodules occurring during the same rheumatic attack often indicate a poor prognosis. Among 96 patients with nodules, 17 had recurrent crops of nodules; 5 of these died during the acute episode (29 per cent), 2 continued to have chronically active disease and died subsequently (12 per cent), and 3 (17 per cent) later succumbed to recurrent attacks, making an over-all mortality rate of 58 per cent. In 79 patients in whom recurrent crops of

Table IV. Mortality follow-up observations on 57 patients with nodules

Years followed	*No. of cases*	*Deaths*
1 to 5 years	35	11
6 to 10 years	13	1
11 to 15 years	4	1
16 to 20 years	5	
Total	57	13

nodules were not observed, the mortality rate was only 25 per cent.

Since the length of follow-up of patients observed during Periods A and B is not comparable, the data for both periods have been combined in a single table.

Long-term prognosis of patients with nodules. Eighteen of the 96 patients died within 9 months or less after the onset of the fatal attack as shown in Table III. Of the remaining 78 patients, 21 were lost to follow-up. The remaining 57 individuals were followed from 1 to 20 years. Among 35 followed from 1 to 5 years, there were 11 deaths, 6 from persistent chronic rheumatic activity and 5 from recurrent attacks of rheumatic fever.

Among 13 patients followed 6 to 10 years, only 1 death occurred because of a recurrence of rheumatic fever. Among 4 patients followed 11 to 15 years, there was also 1 death due to recurrent rheumatic fever. No fatalities occurred among 5 individuals observed 16 to 20 years. These findings indicate that the mortality rate of patients with nodules is highest during the first 5 years and decreases thereafter. Recurrent attacks of rheumatic fever were the cause of death in 5 patients during this period. It is noteworthy that the 2 other deaths which occurred during the 2 subsequent periods (6 to 10 and 11 to 15 years) were also due to recurrences of rheumatic fever. The 7 patients who died as a result of recurrences were not on a prophylactic regimen for the prevention of streptococcal infections. These patients were hospitalized prior to 1950, the year that daily prophylaxis was introduced. The fact that recurrent rheumatic fever developed so many years after the attack of carditis emphasizes the importance of continuing prophylactic measures for the prevention of streptococcal infections throughout life in rheumatic subjects who have had cardiac involvement.

Since death in 7 of these cases was due to recurrent rheumatic fever, it was thought of interest to determine whether, in the absence of overt rheumatic attacks, progressive cardiac damage had developed in patients followed for 1 to 20 years.

Cardiac status of patients with nodules who escaped rheumatic recurrences. Thirty-five patients with nodules were followed for 1 to 20 years. None of these individuals had recurrences of rheumatic fever. After 1 to 10 years, 9 patients had no detectable heart disease. After 1 to 15 years, the degree of cardiac involvement as indicated by a decrease in heart size or disappearance of a significant murmur had diminished in 7 patients. In 17 the cardiac status was unchanged, and in only 2 was there evidence of progressive rheumatic heart disease.

DISCUSSION

The data presented indicate that the severity of rheumatic fever has declined during the past 30 years. During the first half of this period, 1928 through 1942 (Period A), the mortality rate was 16.4 per cent. During the second half, 1943 to 1958 (Period B), the mortality rate decreased to 4.3 per cent.

In 1955 the Cooperative Rheumatic Fever Study, sponsored jointly by the Research Council of Great Britain and the American Heart Association, published observations on 380 children with carditis followed for 1 year after completion of therapy.[13] Only 6 of these 380 patients (1.6 per cent) died. Two of the deaths occurred in centers in the United States and 4 in centers in the United Kingdom. Two of the 4 British children who died had nodules. In 1, only one solitary nodule on the elbow was noted. In accord with previous observations, the incidence of nodules was higher in the British (21.7 per cent) than in the American patients (7.4 per cent).

Table V. Cardiac status after 1 to 20 years of patients with nodules in the absence of rheumatic recurrences

	1 to 5 years	*6 to 10 years*	*11 to 15 years*	*16 to 20 years*	*Totals*
No heart disease	7	2	—	—	9
Decreased heart disease	2	4	1		7
Cardiac status unchanged	11	3	—	3	17
Progressive heart disease	2	—	—	—	2
					35

Three of the 6 patients who died received steroid therapy (1 ACTH and 2 cortisone) and 3 received aspirin. The general conclusion of the Cooperative Rheumatic Fever Study was that the incidence of residual heart disease was the same in the 3 groups that had received the 3 different treatments: ACTH, cortisone, and aspirin. It was noted, however, that nodules tended to disappear more quickly in patients who received steroid therapy than in those who received aspirin. In view of the findings of the Cooperative Rheumatic Fever Study, it seems unlikely that, in our series, the introduction of steroid therapy in 1950 during the last 8 years of Period B was a factor in reducing the mortality rate.

During Period B there were 15 deaths. Twelve of these patients died during the period 1943 through 1949 and 3 died after 1950, the year that antistreptococcal therapy was introduced. Since the follow-up period for patients treated from 1950 to 1958 is relatively short, the effect of streptococcal prophylaxis on the mortality rate during the second half of Period B cannot be determined at the present time.

The most unexpected finding in the series reported in this paper was that although the mortality rate dropped sharply during Period B, the percentage of episodes of carditis accompanied by nodules in Periods A and B remained approximately the same: 68 of 599 attacks of carditis during Period A (11.3 per cent) and 33 of 349 attacks (9.4 per cent) during Period B. In accord with the observations of previous workers, nodules occurred most commonly in patients with rheumatic fever of the chronic or polycyclic type in whom signs of rheumatic activity tended to persist for weeks and months. The prognosis of such patients is always grave and steroid and salicylate therapy usually does little or nothing to arrest the activity of the rheumatic process.

During Period A, the mortality rate in 531 attacks of carditis *not* accompanied by nodules was 16.4 per cent. The mortality rate in 68 episodes *with* nodules was 22 per cent. During Period B, the mortality rate in 316 attacks of carditis *not* accompanied by nodules was 2.8 per cent and that in 33 episodes *with* nodules was 9.1 per cent. During both periods the mortality rate was higher in episodes accompanied by nodules. Since nodules are known to be associated with a severe and protracted type of rheumatic fever, prognosis in patients exhibiting this manifestation should be guarded and the importance of rigid adherence to a prophylactic regimen to prevent recurrent attacks carefully explained to the parents.

SUMMARY

1. During a 30-year period from 1928 to 1958, 948 episodes of rheumatic carditis were observed on the Children's Cardiac Service, Bellevue Hospital.

2. In the first half of this 30-year period from 1928 to 1942 (Period A), 98 deaths occurred in the course of 599 attacks of carditis for a mortality rate of 16.4 per cent. During the second half from 1943 to 1958 (Period B), 15 deaths occurred during 349 attacks of carditis for a mortality rate of 4.3 per cent.

3. The percentage of attacks of carditis with nodules during the two periods showed

no significant difference. During Period A nodules were present in 68 of the 599 episodes of carditis (11.3 per cent) and in Period B in 33 of the 349 episodes of carditis (9.4 per cent).

4. Nodules occurred only in patients with active carditis. Ninety-six patients exhibited nodules on 101 occasions. In 5 patients nodules were observed twice in separate attacks.

5. The severity of carditis was not correlated directly with the number of nodules. The mortality rate among patients with a few nodules, 10 or less, was greater than that among patients with 11 to 30 nodules.

6. Nodules rarely were observed during the first weeks of an acute rheumatic attack. They usually appeared after a month of illness and occurred most frequently in patients in whom rheumatic activity persisted for many weeks or months.

The authors are indebted to Dr. Katherine Dodge Brownell for invaluable constructive criticism.

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ABO isoimmunization: the use of the specific Coombs and heat elution tests in the detection of hemolytic disease

Sol Haberman, Ph.D.,* C. James Krafft, M.D.,

Percy E. Luecke, Jr., M.D., and Richard O. Peach, M.D.

DALLAS, TEXAS

THE COOMBS antiglobulin test is recognized as a springboard to the diagnosis of Rh-Hr erythroblastosis, but most authors have found the results of the direct Coombs test frequently weak or negative in ABO isoimmunization and thus unreliable as a criterion for ABO hemolytic disease.[1-10] This subject has been reviewed recently by one of us. Special emphasis was laid on the specificity of available Coombs antiglobulin sera[11] and showed that unselected reagents may yield poor reactions with antibodies of the ABO system adsorbed in the erythrocytes of the umbilical cord of newborn infants. Haberman and Aguilar[12] have shown that selected antiglobulin sera are reliable in detecting both the adsorbed antibodies of the ABO group and the more reactive Rh antibodies. When such a serum is used, the antiglobulin test holds a pivotal position in diagnosis by alerting the clinician that adsorption of one of the several isoimmunizing factors has taken place.

The difficulties with the direct Coombs test for the diagnosis of ABO hemolytic disease have been due in part to the fact that this reagent is produced and standardized for the detection of the Rh-Hr isoimmunization and not for the detection of antibodies of the ABO blood-tissue groups. Consequently, few workers have been able successfully to demonstrate ABO disease with these reagents.[12, 13] The presence of "naturally occurring" as well as "immune" anti-A and anti-B in the blood of infants, as well as in the mother, created the difficulty of determining when these antibodies were induced by isoimmunization. To solve this problem, Haberman and Hill[14] used the elution test of Landsteiner and Miller[15] as a means of demonstrating the specificity of the antibody causing the damage to the infants' erythrocytes. This method has proved to be routinely applicable and accurate in identifying

From the Immuno-hematology Laboratories of the Department of Pathology and the Department of Pediatrics, Baylor University Medical Center.

Presented at the Ninth International Congress of Paediatrics, July 24, 1959, Montreal, Canada.

**Address, Baylor University Hospital, 3500 Gaston Avenue, Dallas 10, Texas.*

Infants \ Mothers	O	A	B	AB	Total
O	6,653	2,357	632	0	9,642
A	2,354	5,383	206	315	8,258
B	593	265	723	242	1,823
AB	0	262	241	108	611
	9,600	8,267	1,802	665	20,334

Fig. 1. Mother-infant combinations showing ABO groups and potential incompatibilities. The shaded squares indicate the 3,921 potentially incompatible combinations (heterospecific).

the ABO antibodies as well as those produced by other blood group antigens.[12] Munk-Andersen[16] also utilized this elution test in coordination with his direct conglutination test, but most investigators have turned to less specific methods for a presumptive diagnosis of ABO erythroblastosis. The present authors feel, however, that the precision of the elution test properly performed commends it highly for a specific diagnosis of ABO hemolytic disease.

Since the combined Coombs test, performed with selected antiglobulin sera and elution methods, gives an early, definitive diagnosis of the cause of hemolysis in the newborn infant, the clinician may be prepared by the laboratory for the need to observe closely the infant's condition. One does not need to wait for jaundice or other signs in the infant to reveal potential ABO disease. Therefore, this places upon the clinician the need for even closer daily clinical and laboratory examination of the patient.

METHODS

The present study was made on blood samples routinely collected from all mothers delivered at Baylor University Medical Center. Their blood was matched with samples taken from the umbilical cord of their newborn infants. No attempt at selection was made as to type of case, race, or condition of the patients. From Jan. 1, 1956, through Dec. 31, 1958, 20,334 births were studied. The ABO blood groups and Rh-Hr types were determined for both the mothers and the infants. All of the infants' blood samples were tested by the direct Coombs test to see if antibodies adsorbed on the erythrocytes could be noted. The maternal sera were screened for antibodies of red blood cell antigens. Those having positive direct Coombs reactions were further studied by the heat elution method in order to identify the antibody. The Coombs antiglobulin sera used in this study were selected on the basis of their ability to detect adsorbed ABO blood groups in both mild and severe cases of erythroblastosis. The sera giving the greatest sensitivity and specificity were selected.

The ABO determinations. The erythrocytes of both infant and mothers were prepared as 2 per cent suspensions in 0.85 per cent saline. One drop of erythrocytes was placed in each of 3 test tubes (10 times 75 mm.). To the first was added one drop of anti-A serum, to the second, one drop of anti-A_1 (adsorbed-B serum), and to the third, one drop of anti-B serum. The suspension was thoroughly agitated to give good mixture, and a 5-minute incubation period at 22° C. was allowed. The tubes were then centrifuged for one minute at 2,000 r.p.m. and observed micro- and macroscopically for agglutination. In questionable results, the tests were repeated and reverse typing was done with the use of the patients' serum and known A and B blood cells.

The direct Coombs test on erythrocytes from the umbilical cord. A 2 per cent red cell suspension of blood from the umbilical cord was made in saline by breaking the

clot with a wooden applicator and adding the cells that adhered to the applicator to the saline. When unclotted blood was used, a similar suspension was made by adding the whole blood to 2 c.c. of saline. The tube was centrifuged at 2,000 r.p.m. for 2 minutes in an angle centrifuge. By means of a pipette, the supernatant saline was removed and discarded. Two cubic centimeters of fresh saline was then added, and the cells were resuspended. The centrifuge washing was repeated three times. After the third washing, sufficient saline to make a 2 per cent suspension was added. To one drop of this suspension a drop of Coombs antiglobulin serum was added, thoroughly mixed, and allowed to incubate at room temperature for 5 minutes. The tubes were spun at 2,000 r.p.m. for one minute, and then observed for agglutination by carefully and gently resuspending the cells.

The heat elution of antibodies. The blood obtained from the umbilical cord was agitated until sufficient erythrocytes were suspended in the sera to make a heavy suspension. The freed red blood cells were removed by a pipette and separated from the serum by centrifugation. The cells were washed 3 times in 3 volumes of cold saline. One milliliter of packed, washed erythrocytes was added to 1 ml. of fresh 0.85 per cent saline and resuspended. The suspension was subjected to 56° C. in a water bath for 5 minutes. At the end of this period, the suspension was immediately centrifuged at 3,500 r.p.m. for 3 minutes while the temperature of the tube was kept at 56° C. with hot water in the centrifuge cups. The supernatant saline eluate was quickly siphoned off and centrifuged again to remove any traces of the red blood cells. This fluid was then used to test for antibodies. When antibodies were present, agglutination of known adult A or B red blood cells could be shown by mixing one drop of the eluate with one drop of 2 per cent test red blood cell suspensions. If clumping failed to occur a Coombs antiglobulin test was performed to see if nonagglutinating (cryptagglutinoid and agglutinoid) antibodies were present in the eluate. The A and B antibodies could be noted by their selective action on the corresponding group A and B blood cells used in the test panel of blood. The anti-A+B (anti-C) produced agglutination of both the A and B test erythrocytes.

Table I. Summary of findings of ABO incompatibilities from 1956 to 1958

Total mother-infant combinations studied	20,334
Total potential incompatibilities (heterospecific) (1 in 5.18 of all births)	3,921
Cases showing evidence of isoimmunization such as positive direct Coombs and elution tests (1 in 64.3 of all births)	316
Cases with other laboratory evidence of infant R.B.C. destruction	169
Microbilirubin concentrations between 10 and 20 mg.	88
Microbilirubin concentrations over 20 mg.	27
Cases treated by exchange transfusion	26

Table II. Frequency of ABO potential incompatibility and demonstration of isoimmunization by elution test

Total potential incompatibilities	3,921
1. O and B mothers delivered of A or AB children	2,801
Cases showing anti-A eluates	183
Cases showing anti-A+B eluates	96
2. A and O mothers delivered of B or AB children	1,120
Cases showing anti-B eluates	28
Cases showing anti-A+B eluates	9
Total positive elution tests	316

Microbilirubin determinations. The Malloy and Evelyn method[17] was modified for use as a microbilirubin test by decreasing the amount of plasma required from 1 ml. to 0.1 ml. so that heel punctures could be performed on the infants. The results were compared with those obtained with standard bilirubin solutions.* In order to eliminate the use of cuvette spacers and to increase the sensitivity of the method, 1.7 ml. of 50 per cent methyl alcohol was added to the final solution, and the readings were made in terms

*Matheson, Coleman and Bell, Div., Matheson Co., Inc., Cincinnati 12, Ohio.

Table III. Birth order of infants showing evidence of ABO isoimmunization*

First child	75
Second child	99
Third child	78
Fourth or later child	64
Total	316

*All cases proved by positive direct Coombs test and positive elution test with the antibody involved identified.

Table IV. The incidence of highest recorded concentrations of microbilirubin among 113 ABO isoimmunizations

Day of life	*Infants showing clinical symptoms*	*Infants with no recorded symptoms*
Day of birth	0	5
First day	0	10
Second day	8	31*
Third day	17*	14
Fourth day	18*	2
Fifth day	4	0
Sixth day	4	0
Seventh day	0	0
Total	51	62

*Denotes the days after birth that most frequently showed the highest concentrations of microbilirubin, i.e., third and fourth days for clinical cases of ABO hemolytic disease and second day for cases with immunologic findings without clinical symptoms recorded.

of optical density, rather than in per cent of transmission, on a Beckman, Model B, spectrophotometer, with the use of a wavelength of 515 mμ and a sensitivity of 2. The final results were obtained through the use of a K factor which is equal to 95. The milligram per cent bilirubin equals the optical density times 95.

RESULTS

With the use of the program of testing described above, a total of 20,334 mother-infant combinations were studied. Among these were 3,921 potentially incompatible combinations as shown in Fig. 1. These incompatible pairs are the result of heterospecific pregnancies in which the child possesses a blood group antigen not present in the mother. Therefore isoimmunization could occur. Consequently, in this series approximately 1 out of each 5.18 births or 19.28 per cent were heterospecific.

Table I shows the results of the study of these mothers and infants. Only 316 or 1 in 64.3 births (1.55 per cent) showed a positive direct Coombs test. Antibodies were removed from the infant cells and identified, thus establishing the immunologic basis for ABO hemolytic disease. Other tests showed further evidence of erythrocyte destruction, such as a falling hemoglobin level below 15 mg. per cent, reticulocytes above 6 per cent, and/or a bilirubin concentration above 6 mg. per cent, in 169 or 53.43 per cent of the infants. Among these, 88 had bilirubin concentrations between 10 and 20 mg. per cent, and an additional 27 had concentrations over 20 mg. per cent. A total of 26 infants were treated with exchange transfusions because of bilirubin levels which rapidly approached or exceeded 20 mg. per cent.

The elution studies are presented in Table II. Of the 2,801 group O and B mothers who were delivered of A or AB children, 183 or 6.53 per cent showed adsorbed anti-A, and 96 or 3.42 per cent of the infants had the cross-reacting anti-A+B or so-called anti-C of Wiener. Among the 1,120 group O and A mothers delivered of B or AB children, only 28 or 2.50 per cent showed adsorbed anti-B, and 9 or 0.80 per cent of these infants had the cross-reacting anti-A+B. Isoimmunization to the B antigen is apparently less common.

It is well known that the order of birth is important in Rh-Hr hemolytic disease, with the first born rarely affected. Table III, however, illustrates that in ABO hemolytic disease of the newborn infant, the first-born child is also susceptible. It can be seen that 75 first-born infants were affected in the series of 316 infants. The difference between the first through the fourth child is not significantly different.

In contrast to the early intense jaundice usually seen in Rh hemolytic disease, the bilirubin peak concentration in clinical ABO disease often is delayed until the third and fourth days after birth. Table IV shows the

incidence of the highest concentration of bilirubin among 113 of the patients with ABO hemolytic disease studied during the course of their hospital stay. It is of importance to note that some of these affected infants did not reach maximum concentration until the fifth or sixth day. On the other hand, those infants with positive immunologic findings, but without clinical signs of the disease, showed earlier peaks of bilirubin levels. Some of these occurred in the first 24 hours, with the greatest number appearing on the second day after birth.

Fig. 2 shows the maximum bilirubin concentrations, with the clinical cases represented by solid spots and the clinically unaffected but immunologically positive cases represented by hollow spots. It can be seen that the nonsymptomatic children had lower concentrations of bilirubin that peaked earlier than did those of the clinically affected infants.

DISCUSSION

When Coombs serum, previously tested for dependable reactions to the ABO antibodies, is utilized, the results from routine tests of blood from the umbilical cord provide an excellent early warning of possible hemolytic disease. The exact nature of the antibody involved may be determined through the use of the heat elution test on the blood samples showing such positive Coombs reactions. The determination of the antigen concerned provides a method of selecting the proper blood for exchange transfusion within the first 24 hours of the infant's life, rather than delaying treatment as is done when other routines are used. The data herein presented confirm the frequent ab-

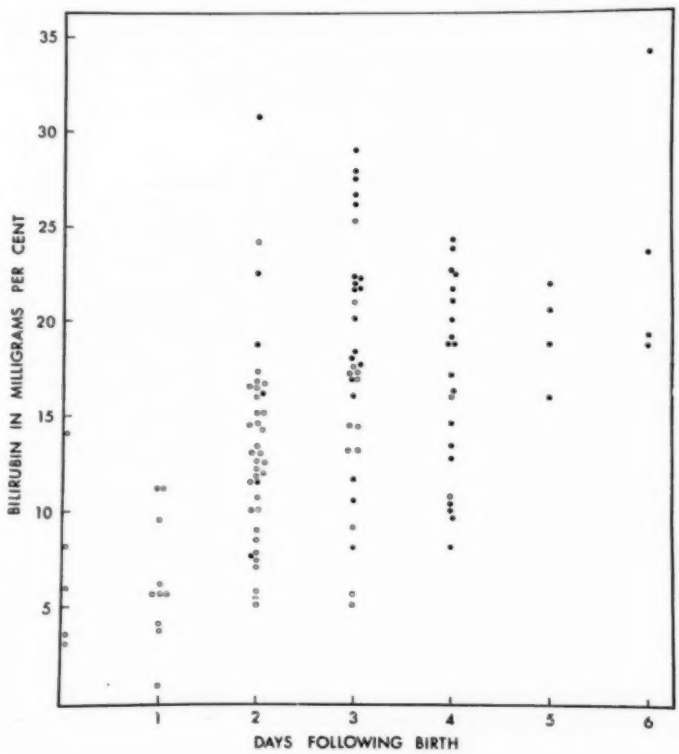

Fig. 2. Day of peak bilirubin concentration in heterospecific ABO mother-infant combinations.

sence of marked jaundice in the early stages of ABO hemolytic disease. Although anemia is not severe in the first 24 hours, our findings show there is usually a steady increase of bilirubin from the time of birth until the fourth day or later. It may reach sufficiently high levels that kernicterus may become a potential hazard. Thus waiting until clinically apparent jaundice occurs, before suspecting hemolytic disease due to the ABO groups, results in an unnecessary lag period between the observable jaundice and the decision to perform an exchange transfusion. In this study, all patients showing positive Coombs and elution tests were observed for a rising serum bilirubin level. These laboratory findings, along with the clinical condition of the patient, were used to determine when an exchange transfusion was indicated. The program of testing and clinical observation described above provides a readily available means of early diagnosis and treatment. Thus the incidence of kernicterus and other damage to the infant due to ABO hemolytic disease can be reduced.

The question of the existence of a blood group C (cross-reacting A+B) of Wiener[18] is reopened in the light of the results of the elution tests presented in Table II. Among the 105 infants that showed anti-A+B eluates were a number of infants of group O primiparas who had no history of previous isoimmunizations by transfusion. Thus, it becomes difficult to ignore the fact that pregnancy with either a group A or B fetus may result in an antibody that agglutinates and is adsorbed by either group A or B erythrocytes. The cross-reacting specificity of these eluates was shown by Haberman and Aguilar.[12] The explanation offered by Wiener that this is due to an antigen C, present in individuals of both A and B but not in group O, seems acceptable at this time.

SUMMARY

A method of early recognition and identification of ABO erythroblastosis is presented. This involves the use of a potent antihuman globulin serum which has been pretested for its ability to detect adsorbed antibodies of the gamma and nongamma globulin varieties. When a positive Coombs test is found on a sample of blood from the umbilical cord, the infant's cells are treated by the heat elution method for the removal of adsorbed antibodies. The eluates thus obtained are tested against a panel of cells containing known antigens, and the specific antibodies are identified. With this early information, the physician is forewarned of the possible development of clinical disease. In our series, which includes over 316 cases of ABO isoimmunization detected by this aproach, it was found that the incidence of ABO isoimmunization approximates that of Rh-Hr incompatibilities. The occurrence of clinical disease in the ABO group was much less frequent, however.

Of the 3,921 heterospecific pregnancies to the ABO system, 316 infants showed positive direct Coombs tests. When heat elution tests were done on blood taken from the infant's umbilical cord, 183 or 57.91 per cent were specific for the A antigen, 28 or 8.86 per cent agglutinated only B erythrocytes, and 105 or 33.22 per cent reacted with both A and B red blood cells and appeared to be the anti-C of Wiener.

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Hilgenreiner measurements of the hip roentgenograms in 247 normal infants 6 and 7 months of age

Follow-up of deviations from "normal"

Lloyd E. Harris, M.D.,* Paul R. Lipscomb, M.D., and John R. Hodgson, M.D.

ROCHESTER, MINN.

THERE IS general agreement that success in the treatment of congenital disease of the hip is enhanced by early diagnosis. Criteria for the early clinical and roentgenographic diagnosis of congenital dysplasia of the hip have been developed over a period of years. Because of the lack of adequate data in regard to the normal and the variations of the normal roentgenographic appearance of the hip in infants, however, dysplasia at this site has undoubtedly been misdiagnosed and unnecessarily treated in many instances. On the other hand, failure to make the diagnosis before the weight-bearing age can only cause less than optimal results of treatment. The study herein reported was designed to add to the knowledge of normal roentgenographic measurements at various age levels. It is a cross-sectional study of a group of normal infants at ages 6 and 7 months with a follow-up of those demonstrating what might have been interpreted as "abnormal" roentgenographic findings.

The most valuable clinical sign for the early detection of congenital dysplasia of the hip, in our experience, has been limitation of abduction of the hips. A negative result with the abduction test in the newborn period and in the early months of infancy does not eliminate the possibility of congenital dysplasia of the hip. The use of this test as a screening method in more than 11,000 infants from the newborn period through 1 year of age will be described in a future publication. By including the abduction test in the routine clinical examination of the newborn infant and healthy child, and by obtaining roentgenographic examinations of

From the Section of Pediatrics, the Section of Orthopedic Surgery, and the Section of Roentgenology, Mayo Clinic and Mayo Foundation.

The Mayo Foundation, Rochester, Minnesota, is a part of the Graduate School of the University of Minnesota.

**Address, Section of Publications, Mayo Clinic, Rochester, Minn.*

those infants who had a positive abduction test, the average age at diagnosis of congenital dysplasia of the hip with dislocation* has been lowered from 14 months to 4 months of age.

While some claim proficiency in interpretation of roentgenograms of the hip in the newborn period, many feel that accurate evaluation is not possible at this age. The value of the roentgenogram increases with the age of the infant and with the concurrent mineralization of the cartilage which permits more accurate visualization and measurement. Several roentgenographic features of this abnormality have been described. We have used the measurements employed by Hilgenreiner[1] (Fig. 1).

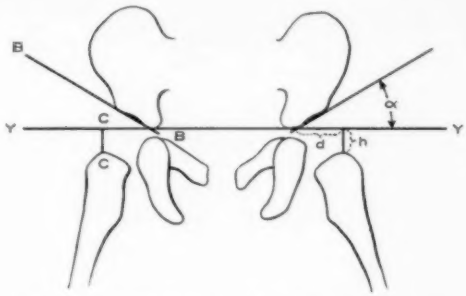

Fig. 1. Drawing to illustrate Hilgenreiner's measurements. *Lines drawn: YY,* line drawn through Y cartilages so as to touch visible tips of ilia; *BB,* line drawn tangentially to visible acetabular face and through medial and lateral bony edges of acetabular face (this line is difficult to draw accurately in the newborn infant because of insufficient roentgenologic definition at this age); *CC,* line drawn from most cephalic point of femoral diaphysis perpendicularly to *YY* line. (Note: *YY, BB,* and *CC* lines are designated as such by the present authors for descriptive purposes.) *Hilgenreiner's measurements:* α, angle between *BB* line and *YY* line, known as acetabular angle; *d,* distance between point of transection of *YY* line by *BB* line and point of transection of *YY* line by *CC* line, generally referred to as the d line of Hilgenreiner; *h,* distance between most cephalic point of femoral diaphysis and point where *CC* line transects *YY* line.

MATERIAL AND METHOD

Roentgenograms of 328 apparently normal infants 4 to 14 months of age were made on an unselected basis in the well-child clinic of the Mayo Clinic and the well-child clinic of the Public Health Department, Rochester, Minnesota, during the years 1947 and 1948. Our study is based on 247 of these infants whose ages were 6 and 7 months. The distribution by age and sex is shown in Table I. The infants were all white and predominantly of northern European descent. The frequency of the presence of the ossification center of the femoral capital epiphysis at the two age levels is recorded in Table II.

*The term "dislocation" is used here to denote both subluxation or incomplete dislocation and luxation or complete dislocation.

Table I. Distribution of infants by age and sex

Age (months)	*Total number of patients*	*Males*		*Females*	
		Number	*Per cent*	*Number*	*Per cent*
6	142	61	43.0	81	57.0
7	105	58	55.2	47	44.8
Total	247	119	48.2	128	51.8

Follow-up studies have been made on those infants with acetabular angles of 30 degrees or more, on those with a discrepancy of 5 degrees or more between the right and left acetabular angles, and on those in whom the ossification center of the femoral capital epiphysis appeared earlier on one side than on the other. The periods of follow-up study ranged from 2 to 10 years.

RESULTS

For each of the three measurements, namely: (1) acetabular angle (α of Hilgenreiner), (2) distance from diaphysis to Y line (h of Hilgenreiner), and (3) distance from diaphysis to acetabulum (d of Hilgenreiner), the mean and the standard deviation were computed separately for each sex, for each of the two ages, and for the right and left sides. In comparison of males with

Table II. Visibility of capital epiphysis

Age (months)	*Males*			*Females*			*Total*		
	Total	*Visible*		*Total*	*Visible*		*Both sexes*	*Visible*	
		Number	*Per cent*		*Number*	*Per cent*		*Number*	*Per cent*
6	61	41	67.2	81	72	88.9	142	113	79.6
7	58	49	84.5	47	46	97.9	105	95	90.5
Total	119	90	75.6	128	118	92.2	247	208	84.2

females, right with left sides, and 6-month-old infants with 7-month-old infants, no material or statistically significant differences were found. It was therefore considered appropriate to group all of the infants together. The distribution in percentages based on all the data available for each of the three factors, with the mean and the standard deviation, are shown in Figs. 2, 3, and 4.

The incidence of visible capital epiphysis is shown separately in Table II for males and females and for age 6 months and age 7 months. The rate of occurrence in the females was significantly higher than in the males (92.2 per cent as compared to 75.6 per cent). Epiphysis was significantly more visible in the 7-month-old infants than in the 6-month-old infants, the difference being greater for the males than for the females (17.3 per cent for the males compared to 9.0 per cent for the females).

Acetabular Angle (α of Hilgenreiner). Fig. 2 shows the distribution in percentages of the infants according to the magnitude of the acetabular angle.

It is our opinion that the measurement of the acetabular angle, as well as other measurements made in the roentgenogram of the hip, should be interpreted with reference to the frequency distribution of the normal at various age levels. Thus, if the value for the acetabular angle is more than two standard deviations from the mean, one should evaluate this finding in relation to other data as evidence that a pathologic condition exists in a particular individual. It is apparent that one should not designate a definite value below which the acetabular angle would be considered "normal" and above which it would be considered "pathologic." The tendency in the past has been to state a definite acetabular angle as "normal" and then consider any angle greater than this as abnormal.[1-5] The "normal" thus stated has ranged from *about* 20 degrees[1] to 30 degrees.[2] We would agree with Caffey and associates[6] who stated, "It is obvious that 30 degrees is a fallacious value for separating normal angles from enlarged angles in this population." We would again call attention to the difficulty in securing accurate measurements in the neonatal period, however, and thus emphasize the limited value of the acetabular angle as a diagnostic criterion for dysplasia of the hip at that age. We would reiterate that it is desirable to use the acetabular measurements in later months much as the physician uses height-weight tables. Thus, in an infant of 5 to 7 months of age one would recognize that an acetabular angle of 31 degrees falls beyond two standard deviations and would wish to evaluate the significance of this finding, just as one would wish to evaluate a child's weight that was two standard deviations above or below the median for his age and height.

In conjunction with other findings, the difference between the right and left acetabular angles may be of some assistance in making a tentative diagnosis of congenital dysplasia of the hip. A difference of 5 degrees between the two angles falls beyond two standard deviations. This measurement, as are the others, is of most value in diagnosing unilateral dysplasia of the hip.

Diaphysis to Y line (h of Hilgenreiner). The distribution in percentages of the infants according to the diaphysis-to-Y-line

measurement, with the mean and the standard deviation, is shown in Fig. 3.

Placing the child accurately in a position with the legs in full extension and knees together is desirable for this measurement. Reasonably adequate measurements can be made, however, even if the infant is not in this exact position. The range of this measurement is fairly wide, with two standard deviations giving the extremes of 6.3 mm. and 12.3 mm. for the range in this group. Hilgenreiner[1] states that the distance from the diaphysis to the Y line is, in general, 1.0 cm. in the normal infant. Although the data are not included in this report, it was noted that the difference between the right and left diaphysis-to-Y-line measurements in each infant within two standard deviations was less than 2 mm. Thus, the difference between the right and the left sides may be of assistance when used in conjunction with other findings to determine whether there is unilateral dislocation.

Diaphysis to acetabulum (d of Hilgenreiner). Fig. 4 shows the distribution in percentages of the patients according to the distance from the diaphysis to the acetabulum. Comparison of the right and left sides with respect to this measurement showed again that, as with the distance from the diaphysis to the Y line, the difference between the right and left sides was less than 2 mm. and within two standard deviations. This comparison was of special value when used with other measurements to evaluate unilateral displacement. According to Hilgenreiner,[1] the distance from the diaphysis to the acetabulum is 1.0 to 1.5 cm. in the normal infant.

Presence of capital epiphysis. Delay in the appearance of the capital epiphysis of the femur may be significant in assessing the roentgenogram of the infant suspected of having dysplasia of the hip. This ossification center may appear between the second and the ninth month of age, and, as with other ossification centers, appears earlier in the female than in the male (Table II). Delay in appearance of ossification centers in the capital epiphysis, when unilateral and evaluated in association with other findings, may help to establish the diagnosis of unilateral dysplasia of the hip.

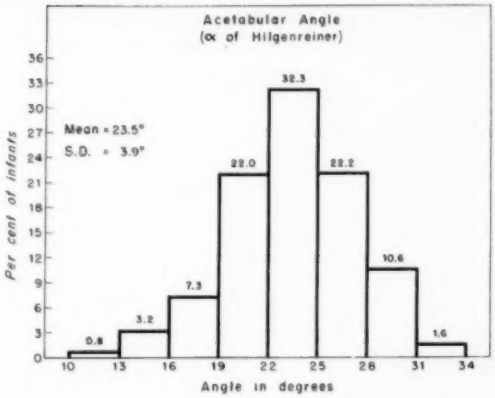

Fig. 2. Distribution in percentages of infants according to magnitude of acetabular angle (*a* of Hilgenreiner).

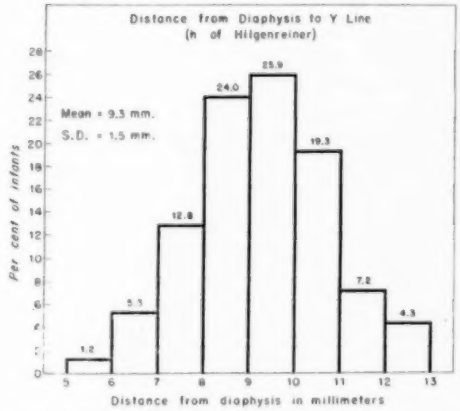

Fig. 3. Distribution in percentages of infants according to the distance from diaphysis to *Y* line (h of Hilgenreiner).

FOLLOW-UP STUDIES

The entire group of children was under observation for 2 to 10 years; the average period was 7 years. All were observed for at least 1 year after the weight-bearing age, and in none did dislocation of the hip develop. In one child the "routine" roentgenograms were taken at 9 months of age. A

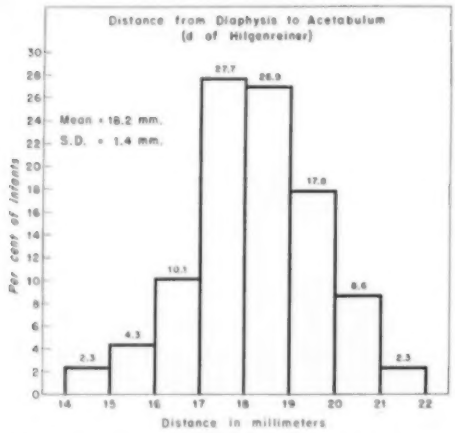

Fig. 4. Distribution in percentages of infants according to the distance from diaphysis to acetabulum (d of Hilgenreiner).

difference in thickness of the capital epiphyses was evident at that time, the right side being definitely thinner (7.5 mm.) than the left side (11 mm.). It had been observed that the infant had "a tendency to contraction of the hips and to hold the legs in the fetal position" in the neonatal period. The abduction test per se was not being done or recorded as part of the neonatal examination at that time (1947). A sternocleidomastoid tumor and torticollis had developed and the child was being observed for this condition by an orthopedic surgeon. Because of continued "tendency to contraction of the hips" a roentgenogram made at 4 months of age led to a diagnosis of "congenital dislocation of the right hip." At that time the right acetabular angle measured 40 degrees and the left acetabular angle 30 degrees. The capital epiphysis was evident on the left and not on the right. A "canvas diaper splint" (Frejka) for maintenance of abduction had been prescribed at that time (4 months of age) and had been worn until the time of the "study" roentgenogram, a period of 5 months. At this time (9 months of age) the acetabular angle measured 20 degrees on the right and 23 degrees on the left. The splint was discarded at 9 months of age. No abnormalities were noted in the roentgenograms of the hips taken at 2 years of age. The child had a normal gait at 10 years of age.

A group of 30 infants in this study who had had one or more of the roentgenographic measurements and who by some criterion might have been thought to have dysplasia of the hip has been observed clinically for periods of time ranging from 2 to 10 years; the average time has been more than 7 years (Table III). Except for the one infant just mentioned, none had therapy for disease of the hip and all had a normal gait during the period of observation. This group includes those who had an acetabular angle (or angles) of 30 degrees or more, those with a difference of 5 degrees or more between the right and left acetabular angles, and those with a difference between the two sides in respect to the presence or size of the capital epiphyses. Fourteen of the 30 children were examined at 10 years of age and found to be normal both clinically and roentgenographically. Only one child had what might have been interpreted at that time as suggestive evidence of dysplasia. This child is the one in the classification of acetabular angle of 30 degrees with concurrent delay in the appearance of the capital epiphysis (Table III). Roentgenograms were made at 7 months of age when the right acetabular angle measured 30 degrees and the left 27 degrees. The capital epiphysis, although only 3 mm. thick, was clearly visible on the left but was not visible on the right side. The infant was seen regularly in the well-child clinic and no abnormalities were noted. At that time (1947 and 1948) the abduction test was not performed as part of the routine physical examination in the well-child clinic. The patient is now 10 years of age and no abnormalities have been noticed.

COMMENT

Data on the normal range of the roentgenographic findings at various age levels in infants have not been adequate and thus interpretations have varied considerably. In our experience, where the average age at diagnosis of congenital dysplasia of the hip

with luxation has been at 4 months of age, the roentgenographic criteria have been essentially the same as in the infants of 6 and 7 months of age in this study. Hilgenreiner measurements for each month during early infancy would be of value, but we have been reluctant to conduct further roentgenographic surveys because of the present concern over undue or unwarranted x-ray exposure.

It would seem that if all newborn infants were subjected to adequate clinical or routine roentgenographic examination of the hips, or to both examinations, congenital dysplasia of the hip would always be discovered in the neonatal period and early treatment instituted. Although we have been able to make the diagnosis in the newborn period, twice as many infants have shown signs of dysplasia and dislocation at a later age in infancy. As mentioned, we feel that interpretation of the roentgenogram of the newborn infant is extremely unreliable and may be faulty from either a negative or a positive standpoint. The roentgenographic signs become more valuable as the child grows older.

We would like to reiterate that a negative result with the abduction test in the newborn period does not rule out dysplasia and potential dislocation of the hip. Also, as shown by Caffey and associates,[6] routine roentgenographic examination of the newborn infant fails to reveal dysplasia and potential dislocation of the hip in some instances. Two of the infants in their study, who had no roentgenographic evidence of dysplasia in the newborn period, were found to have dislocation when roentgenograms were made at 6 months of age.

In our experience, clinical examination combined with the roentgenographic examination has been effective in the early detection of dysplasia and dislocation of the hip. The abduction test should be included in the monthly physical examination of the healthy infant; when the result is positive, roentgenograms of the hips should be made to assist in determining if dysplasia is present. When the diagnosis cannot be established, one may wish to observe the child closely until the findings are more definite or until the hips "declare themselves." We would urge that the roentgenographic findings in an instance of possible dysplasia be interpreted in relation to normal values for the infant's age.

SUMMARY

The Hilgenreiner measurements of roentgenograms of the hips were determined for a group of infants 6 and 7 months of age. Also, data on the presence or absence of the

Table III. Unusual findings or measurements

	Number	*Male*	*Female*	*Years followed*		*Negative clinical and x-ray examination at age 10 years*		
				Range	*Mean*	*Number*	*Male*	*Female*
Acetabular angle								
> 30° (31°-34°)	8	1	7	2 to 10	6	3	1	2
30°	4	1	3	3 to 10	7½	3	1	2
30° with concurrent delay in appearance of capital epiphysis	1	0	1	10	10			
Difference, R. to L., of 5° or more (5°-7°)	3	2	1	5 to 10	7	3	2	1
Capital epiphysis								
Visible on one side but not on other	5	5	0	2 to 10	6	3	3	0
Marked difference in size*	9	5	4	2 to 10	6	2	1	1

*See text in regard to other unusual x-ray findings in one of this group.

capital epiphysis were obtained, and follow-up studies of those infants whose measurements deviated from the "average" were made. It is suggested that Hilgenreiner measurements be used for interpretative purposes in relation to two standard deviations from the mean.

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Balantidiasis in infancy

Review of the literature and report of a case

Norman C. Woody, M.D.,* and Hannah B. Woody, M.D.

NEW ORLEANS, LA.

HUMAN infection with *Balantidium coli*, the only pathogenic ciliate found in man, is relatively rare. It was first described by Malmsten in 1857.[1] Since then, 722 cases[1-47] have been described in the literature available to us. Of these, 62 were instances of infection in children under 12 years of age, 3 of whom died. In the United States, 61 cases have been reported from 16 states; 8 were children.[1, 6, 7, 10, 14, 16-19, 21, 22, 24] The only report in American pediatric literature appeared in 1918.[2]

Several considerations prompt this report. Although unusual in our country, the disease is often severe. Increased global travel favors acquisition of any disease related to food and water contamination. Antibiotic therapy has, in recent years, provided safe, effective treatment. This is the first report of the disease in so young an infant, the youngest earlier patient being 1 year old.[3]

PARASITOLOGY

B. coli is the largest of the intestinal protozoa. Both trophozoite and cyst stages are observed in humans; the former are generally associated with diarrhea, the latter with formed stools during asymptomatic periods. The trophozoite (about 100 × 60 mμ) is variously described as egg-, boat-, or pear-shaped. The anterior end is somewhat narrow. In an unstained stool suspension they appear as large, oval, hyaline or slightly bluish objects which are readily seen under low-power magnification as they glide rapidly through the microscopic field. The constantly moving cilia are visible under high-power magnification. A distinct characteristic is the large, kidney-shaped, macronucleus which may be located in various places within the organism. It can be observed in living as well as in fixed specimens stained with iodine or iron-hemotoxylin. It serves to differentiate this species from free-living ciliates which may contaminate fecal specimens or containers. Other internal structures may be present. Two contractile vacuoles are generally visible, a micronucleus which may be found near the concavity of the macronucleus, and the funnel-shaped cytostome which may be seen at the anterior end. Food vacuoles are usually present. The cysts (about 50 × 60 mμ) are spherical or ovoid, have a green or yellow color, and possess a doubly outlined wall. When first formed, they contain a single balantidium which can be seen to revolve slowly within the cyst membrane. In older

From the Department of Pediatrics, Tulane University School of Medicine, the Charity Hospital of Louisiana at New Orleans, and the Memorial Hospital, Corpus Christi, Texas.

**Address, Department of Pediatrics, Tulane University School of Medicine, 1430 Tulane Avenue, New Orleans 12, La.*

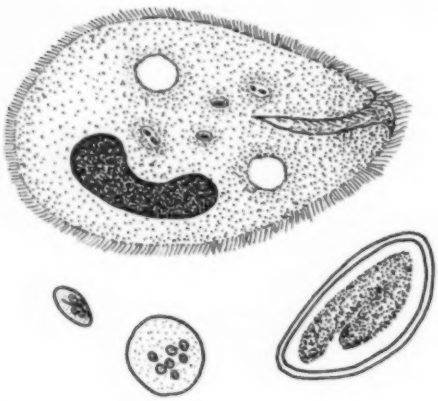

Fig. 1. *B. coli* trophozoite contrasted with Giardia cyst, *Endamoeba coli* cyst, and Enterobius egg.

cysts the cilia are lacking, and only the macronucleus is clearly visible within a mass of cytoplasmic material. These cysts are seen in the stools of less than 10 per cent of infected individuals.

When stool parasite surveys have been done in various parts of the world, balantidium has been found in about 1 out of 1,200 examinations.[4-8]

EPIDEMIOLOGY

Infection with a Balantidium, apparently identical with that found in man, has been reported to be widespread in pigs and monkeys. Despite abundant infections in swine, the role of the pig in transmission of the disease to humans is uncertain since a history of contact with pigs is present in only 14 per cent of the cases reviewed. Also, it seems odd that packing house workers are seldom infected. One of the largest series (87 cases) occurred in Moslems who had no known contact with pigs.[7] Contamination of food and water is generally accepted as a mode of human infection. Flies have been suggested as vectors without valid proof. Direct transmission in humans has been described in "epidemics" among inmates in mental institutions.

Occurrence in man may relate to factors other than contact. Masing,[9] in 1929, found a lack of free gastric hydrochloric acid in 12 of 14 cases. Neilson[48] noted that the organism in culture died rapidly when a pH of 5 was attained. Logan[10] observed 3 cases occurring with pernicious anemia and achylia gastrica. These observations may explain why attempts to transfer Balantidium from both pigs and monkeys to human volunteers have not been successful.

Concomitant infections with bacillary or amebic dysentery have been postulated to produce lesions in human subjects.[1] Instances of lesions from Balantidium alone have, however, been documented.[11, 12] Most of the reported cases have occurred under circumstances which might reduce host resistance, i.e., enteric infections, additional parasite invasions, malnutrition, systemic disease, and the like.

PATHOLOGY

Lesions are confined to the large bowel, especially the cecum, the sigmoid, and the regional lymph nodes. Ulcerations of the mucous membrane occur; these are discrete, irregular, and undermined, with the intervening mucosa either normal in appearance or slightly hyperemic. Thus the gross lesions resemble those of amebiasis. The ulcers may be pin-point size or larger and shallow or deep into the muscularis. "Silent" perforations have been reported.[3] Balantidia may be seen collected in nests in the tissues about the ulcers and often invade regional lymphatics.

CLINICAL MANIFESTATIONS

Clinical manifestations are those of enterocolitis. Asymptomatic cases can occur and appear to do so with greater frequency in children. Of 28 children, for whom sufficient data were present, 10 were asymptomatic; in contrast, only 3 out of 156 adult patients were free of symptoms. Symptoms occurred in the following order of frequency: diarrhea, dysentery, abdominal pain, vomiting, and loss of weight. Weight loss may be conspicuous in adults. One patient lost 70 pounds. Another gained 112 pounds following eradication of the parasite.[14] Duration of infection varied from 4 months to 26 years in

adults and from 1 week to 4 years in children. The fatality rate of balantidiasis in 1901 was reported to be 30 per cent, but analysis of more recent cases treated with carbarsone and Diodoquin reveal a rate of 5 per cent. No reports of fatality rates could be found since tetracyclines became available for treatment.

On occasion, the diagnosis can be suspected at the bedside because of a peculiar "pigpen" odor of the stools. Specific diagnosis rests on demonstration of trophozoites or cysts in the stools. With diarrhea, trophozoites are usually abundant in direct fecal smears if the stools are examined promptly; they can disintegrate in a short time and may not be seen if the search is delayed. Zinc sulfate flotation will not elevate trophozoites, but it is useful in discovering cysts. Sigmoidoscopy may demonstrate characteristic bowel lesions and is especially useful in obtaining good diagnostic specimens and in following results of therapy.

TREATMENT

At present the tetracyclines appear to be the drugs of choice. Equally good results have been reported with oxytetracycline,[25, 26, 31] and chlortetracycline.[27, 29] Oxytetracycline in divided doses of 50 mg. per kilogram per day is said to relieve symptoms and eradicate parasites quickly. Relapses have not been reported within 6 months of cessation of therapy. Chlortetracycline (25 to 50 mg. per kilogram per day) has also been reported to be effective. Reinfections have occurred after the use of the tetracyclines, but treatment failures and relapses, which were frequent with older methods, have not been published.

Until recently, carbarsone and Diodoquin were most frequently used. Resistant cases were treated with chiniofon, emetine, or oil of chenopodium. One death from the use of chenopodium in the treatment of a child has been reported.[15]

CASE REPORT

S. A. A., a 5-month-old Latin-American girl, was admitted to Memorial Hospital, Corpus Christi, Texas, in May, 1949. She was born after a normal pregnancy and delivery; she weighed 6 pounds. She had been well until just prior to the current illness which began when she was 3 months old. Her parents and grandparents lived together in a nearby town. There were no pigs on the premises and no known contact with swine had been had by any member of the family for at least 4 years. None of the adults had had diarrhea or gastrointestinal symptoms. There was an indoor toilet and city water in the home. The infant had received an evaporated milk formula carefully prepared according to adequate, printed instructions from the local well-baby clinic.

In March, 1949, she had developed fever, followed by diarrhea. The latter was intermittent for a few days and then became severe enough to require hospitalization for a week. Diarrhea recurred almost at once after the child returned home and continued with 4 to 6 loose, foul stools daily until she was readmitted in May. For 4 days prior to admission she had vomited the greater part of her meals. In the interval, the mother, on advice of relatives and friends, had given her a variety of formulas.

When she was admitted, she was grossly underweight (6 pounds 15 ounces) for a 5-month-old infant, was badly dehydrated, and was apparently in shock. Her temperature was 103° F. rectally, her pulse was 160 per minute, and her respirations 36 per minute. The remainder of the physical examination was essentially negative except for a grayish pallor and the fact that her soiled diaper had the odor of a pigsty. Numerous trophozoites of *B. coli* were found in a fecal suspension. A moderate hypochromic, normocytic anemia was present; evidence of megaloblastic anemia was lacking in the blood smear. Gastric analysis was not done. Pathogenic microorganisms did not appear in the stool cultures.

Shock and electrolyte imbalance were corrected and by the third day she was afebrile and moderately well hydrated. Because of malnutrition, a month was spent in careful supportive efforts. At the end of that period the stools were still loose and showed Balan-

tidium; her weight was only 8 pounds. Carbarsone was prescribed in a dose of 12.5 mg. twice daily. At the initial dose there was a miscalculation and 10 times the desired amount was administered. The drug was stopped for 10 days and then resumed at 12.5 mg. twice daily and given for 10 days. The stools became normal for the first time and no Balantidia were found in repeated stool examinations prior to discharge 1 month later. She was free of symptoms for the final month and weighed nearly 10 pounds at discharge.

A follow-up visit was arranged when the child was 5 years old, routine care having been provided locally in the interval. The mother reported that the child had been in excellent health and had had no diarrhea or gastrointestinal complaint during this period. Her physical examination was within normal limits and she weighed 38.5 pounds. Stools were again negative for *B. coli.*

SUMMARY

Balantidium coli infection in a malnourished 5-month-old infant was treated with carbarsone, resulting in eradication of the parasite. She is believed to be the youngest patient with this condition on record.

The disease may be encountered in all parts of the world. Air travel may increase opportunities for exposure. Unless considered, it can be overlooked as a cause of diarrhea. Immediate, proper examination of fresh stools should easily reveal the trophozoites in acute cases.

At present, treatment with tetracyclines appears to be the preferred method.

The epidemiology of balantidiasis is still obscure.

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Pyloric stenosis in premature infants

Miriam G. Wilson, M.D.*

LOS ANGELES, CALIF.

CONGENITAL pyloric stenosis is relatively infrequent in premature infants. The actual incidence is unknown since in many of the large reported series the weight at birth is not given. Of the 460 cases of pyloric stenosis reviewed by Kehl and Lange,[1] 17 or 3.5 per cent occurred in premature infants. Miller and Friesen[2] reported that of their 87 infants, 4 (4.5 per cent) were premature by gestational age. An incidence of prematurity of 5.8 per cent was found in Renvik's[3] series of 137 cases of pyloric stenosis.

During the 2½ years from 1956 to mid-1958, 5 of 3,813 premature infants in Los Angeles County Hospital Nursery had surgical repair for pyloric stenosis. All of these infants with the exception of Case 1 were seen by the author. These cases are presented to draw attention to pyloric stenosis as a diagnostic possibility in premature infants, to describe the clinically progressing symptomatology in infants observed daily from birth, and to point out dissimilarities of the illness in premature and full-term infants.

CASE REPORTS

Case 1. A Caucasian girl, weighing 1,475 grams, was born to a mother who had been delivered of 1 child previously. Moderately severe erythroblastosis fetalis with hyperbilirubinemia was treated by 2 exchange transfusions. The infant appeared well in the second week of life with no evidence of kernicterus.

Feedings were gavaged until the twenty-sixth day of life when nipple feedings were offered regularly. From the thirty-fifth day, the infant vomited between feedings in gradually increasing volume and frequency. Following propping in the Fowler position, thickening of the feedings, substitution of breast milk for cow's milk, and medication with belladonna-phenobarbital vomiting lessened temporarily, only to recur as before. Never was the emesis projectile or bile stained, although on occasion it was streaked with brown blood.

The infant was extremely hungry and ate eagerly at all feedings. From the day of birth the stools were small and infrequent, becoming green, mucoid, and loose "starvation" stools at about the sixtieth day of life. Anorexia appeared at this time. Gain in weight was adequate up to the sixty-third day. Approximately 6 per cent of the body weight was lost during the next 10 days. Parenteral fluids were given throughout the period of vomiting.

The upper gastrointestinal tract was studied radiologically on the forty-third and the fifty-first days in an attempt to solve conflicting clinical opinions. The studies were interpreted as probably normal, although they suggested a partial pyloric obstruction. By the seventieth day of life, a pyloric tumor was felt.* Neither abnormal distention nor hyperactive peristalsis was present. The general state of health was poor, although

*Present address, Department of Pediatrics, University of California Medical Center, Los Angeles 24, Calif.

*The date that the pylorus was first palpable is unknown.

Table I. Laboratory data prior to the operation

Case no.	Age (in days)	Hgb. (Gm. %)	W.B.C. per mm.³	Urine analysis	CO_2 (mEq./L.)	Cl (mEq./L.)	Na (mEq./L.)	K (mEq./L.)	NPN (mg. %)
1	70	11	--	--	31	--	--	4.2	35
2	54	11	3,550	--	33	87	--	3.2	BUN 22 mg. %
					(Fluids containing Na, Cl, and K given)				
					35	96	138	3.2	BUN 13 mg. %
3	32	15	7,400	Normal	32	--	137	4.6	19
4	35	15	9,900	Normal	34	--	154	5.5	34
	40	--	--	--	40	--	146	4.7	--
5	87	13	--	Normal	31	--	137	4.6	--

hydration was normal. Mild alkalosis and hypokalemia were present (Table I). Radiologic examination of the pylorus demonstrated marked pyloric obstruction and abnormally increased gastric peristalsis.

Three days later, after an illness of 38 days, the infant, now weighing 1,900 grams, was operated on and found to have a marked pyloric stenosis. In spite of the Ramstedt pyloromyotomy, vomiting continued unabated to the fourth postoperative day when death ensued. Final diagnoses after postmortem examination were malnutrition and inanition due to congenital pyloric stenosis (repaired). The lungs were diffusely atelectatic. Kernicterus was not present.

Case 2. A 1,245 gram Mexican girl was born Dec. 20, 1956. The mother had been well throughout her pregnancy and had previously been delivered of 2 normal children. Moderate respiratory distress was present at birth. On the second day of life, oxygen was discontinued and gavage feeding was begun. Transient cyanosis, which lessened when oxygen was administered, appeared throughout the first week but was otherwise noteworthy only for moderate "physiologic" jaundice.

On the sixteenth day of life, the infant was hyperpneic, persistently cyanotic, and lethargic. An x-ray of the chest and abdomen did not disclose any abnormality. Intensive treatment with chloramphenicol was given in view of the clinical diagnosis of bronchopneumonia. Cyanosis and hyperpnea gradually disappeared. On the thirty-sixth day the infant, now vigorous and gaining weight, began to feed by nipple.

On the thirty-seventh day, the infant, who weighed 1,700 grams, began to vomit. Vomiting, at first intermittent and of small volume, gradually increased until on the forty-eighth day it occurred at least twice daily and consistently from 5 to 10 minutes after feeding. "Overflow vomiting" or chalasia was thought to be a possible diagnosis. Gastric lavage before feedings and a decrease in the volume of the formula were followed by improvement for 1 or 2 days. Stools, small and infrequent since birth, were not observed from the fiftieth day to the time of the operation 5 days later.

Weight was gained well to the twenty-ninth day of life. From that day to the operation on the fifty-fifth day, however, 13 per cent of the total body weight was lost.

A pyloric tumor was felt on the fifty-fourth day. Visible gastric peristalsis, but no unusual distention, was evident. The infant was lethargic and pale and breathed irregularly and shallowly. She was adequately hydrated, however. Mild alkalosis, hypokalemia, and hypochloremia were present (Table I). A radiologic gastrointestinal study showed a greatly narrowed, "string-like" pyloric canal and delayed gastric emptying,

confirming the clinical diagnosis of pyloric obstruction, most likely congenital pyloric stenosis.

On the fifty-fifth day of life, corresponding to the eighteenth day of gastrointestinal symptoms, the infant was operated on. Her weight was 1,700 grams. The pyloric stenosis was repaired by Ramstedt pyloromyotomy under local Xylocaine anesthesia.

Recovery was rapid in the postoperative period. Since peristalsis was active by 24 hours after the operation, nipple feedings were begun and were well tolerated thereafter. On the seventy-first day of life, the fifteenth postoperative day, the infant, who weighed 2,300 grams, was discharged. In the following year the infant was treated four times for bronchopneumonia and bronchiolitis. No dysfunction of the gastrointestinal tract was noted.

Case 3. A 1,390 gram Mexican girl was born Feb. 6, 1957, after an uncomplicated pregnancy, estimated at 31 weeks, to a mother who had previously been delivered of 6 children. Initial respiratory distress was present. Gavage feedings begun on the second day were well tolerated. Moderate "physiologic" jaundice was present during the first week.

On the twenty-second day, the infant, who weighed 1,530 grams, was placed in a crib and fed by nipple. Two days later regurgitation occurred once and once again on each of the 2 following days. Vomiting thereafter was more frequent, appearing at any time from immediately after feeding to an hour later and ceasing temporarily after formula changes, head-up positioning, and belladonna-phenobarbital medication. The infant ate eagerly at all times. Although slightly small in volume, stools occurred at relatively normal frequencies throughout this period. Gain in weight was adequate until the twenty-fourth day, after which time 5 per cent of the total body weight was lost in the 8 days remaining until the operation.

On the twenty-ninth day of life, 6 days after the onset of vomiting, a pyloric mass was palpated. Since all clinicians did not agree that a mass was present, an upper gastrointestinal x-ray study was done. The only abnormality was moderate gastric retention. The final conclusion was "a hypodynamic upper gastrointestinal tract with normal architecture."

Vomiting was never projectile. Increased gastric peristalsis and distention were not seen. The infant was active, vigorous, and only mildly dehydrated. Supplemental parenteral fluids had been given during the period of vomiting. There was a mild alkalosis (Table I).

On the thirty-third day, after 9 days of vomiting, a Ramstedt procedure under local Xylocaine anesthesia corrected the obvious pyloric stenosis. Weight at the time of the operation was 1,500 grams. At 18 hours postoperatively, nipple feedings were offered and taken well. Weight was gained on the second postoperative day; there was an increase of 900 grams during the next month. The infant was discharged on the sixty-first day; she weighed 2,330 grams. No serious illnesses or gastrointestinal symptoms occurred during the 2 months of outpatient supervision.

Case 4. On Feb. 19, 1957, a 1,280 gram Caucasian girl was born prematurely as a consequence of partial placenta previa. The mother had been delivered of 2 children previously. The infant was in moderate respiratory distress for 24 hours after birth. Gavage feedings were begun at 2 days of age. Jaundice during the first week of life was considered to be physiologic. A moderate loss of weight occurred within the first week, after which time the infant rapidly regained the lost weight. When the infant was 26 days old, nipple feedings were begun.

On the thirty-first day the infant, who weighed 1,530 grams, vomited for the first time. Subsequently, intermittent vomiting, always of large volume, occurred at any time after feedings. There was an occasional, asymptomatic 24-hour period. The infant's appetite was voracious at all times. Stools were normal, although questionably diminished in volume, up to the thirty-fifth day of life. No stools then appeared until after the operation 7 days later. During the vomit-

ing interval, 10 per cent of the body weight was lost.

On the thirty-fifth day, 4 days after the appearance of vomiting, a pyloric tumor was felt. Since all clinicians again did not agree that a mass was present, the observation period was extended. There were no prominent gastric waves or significant distention. Laboratory studies showed moderate alkalosis (Table I). Roentgen studies of the upper gastrointestinal tract on the thirty-fourth and the forty-first days were interpreted as normal with the exception of a 3-hour gastric Lipiodol retention in the second study.

On the forty-first day, 10 days after vomiting appeared, a pyloric tumor was palpated very easily. The infant weighed 1,420 grams at this time. The following day an operation under local anesthesia disclosed pyloric stenosis, and a Ramstedt operation was performed.

At 24 hours postoperatively, feedings were begun and well tolerated except for 1 initial emesis. An excellent gain in weight began on the fourth postoperative day. Unfortunately, however, the postoperative course was complicated by a surgical wound infection from which *Escherichia coli* were cultured. In spite of attempted surgical closure, wound dehiscence persisted; healing eventually was by tissue granulation. The infant was discharged on the ninetieth day and weighed 2,750 grams. On an outpatient clinic check at 8 months of age this child was found to be well. Plans were made for a later elective repair of the incisional hernia and of bilateral inguinal hernias then present.

Case 5. A Negro girl, weighing only 879 grams, was born Feb. 1, 1958. Complicating the pregnancy of the primiparous mother were acute pyelonephritis and ruptured fetal membranes for 40 hours prior to delivery. In spite of the very small size of the infant, she was in good condition at birth.

On the twenty-first day of life the infant forcibly vomited twice. She subsequently was cyanotic and apneic but improved after ammonia inhalation. She seemed to be well during the following 4 days, although she regurgitated a small amount of formula once each day. On the thirty-first day, in the absence of recent feeding or vomiting, she became cyanotic, apneic, and subsequently hyperpneic. Pneumonia, possibly secondary to aspiration, was diagnosed. Throughout the next 15 days, intermittent but minimal regurgitation occurred, though never of a sufficient degree to alarm the nursing or medical staff. Approximately a week without vomiting then followed. From the fifty-eighth to the eightieth day, although an occasional emesis was noted, symptom-free periods of up to 24 hours intervened. Nipple feedings were begun on the seventy-seventh day.

From the eightieth to the eighty-eighth day and also the day of the operation, vomiting of volumes of 5 to 10 c.c. occurred consistently at least once daily. Vomiting appeared at any time from immediately following feeding to just before the next feeding. The vomitus contained formula, small amounts of mucus, and, on the day prior to the operation, "coffee ground" blood. The infant was constantly hungry and was taking bottle feedings eagerly throughout the entire period. Stools usually occurred once daily and were small in volume.

Weight was gained steadily up to the eighty-fifth day of life, at which time the infant weighed 1,560 grams. During the next 3 days, 4 per cent of the body weight was lost.

On the eighty-sixth day a Lipiodol x-ray study of the upper gastrointestinal tract showed moderate gastric distention and a small amount of gas in the small bowel. The chest, also visible in the x-ray, was normal. Upper abdominal distention was significantly increased on the eighty-seventh day, the day prior to operation. Prominent gastric waves had not been seen at any time. A small pyloric mass, however, was very easily felt. At this time the infant was active, adequately hydrated, and mildly alkalotic (Table I).

On the eighty-eighth day, 67 days after the onset of vomiting, the infant, during the operation, was found to have a typical pyloric stenosis. It was repaired at that time by a pyloromyotomy. Weight at this time was 1,500 grams.

During the first postoperative day nipple feedings were begun and stools were observed. Weight was gained steadily from the third day. No gastrointestinal dysfunction occurred. Bronchopneumonia in the fourth month prolonged hospitalization. At 5 months of age, the infant was discharged; she weighed 3,260 grams. There has been no return to the outpatient clinic.

RESULTS

General characteristics and certain clinical data of 5 premature infants with congenital pyloric stenosis are summarized in Tables II and III. All were females and only one was a first-born child. The presenting and important sign of gastrointestinal disturbance was vomiting, which appeared from 3 to 5 weeks after birth and tended either to appear or to increase significantly a few days after the infants had changed from gavage to nipple feedings. Vomiting was inconstant in amount, frequency, and time relationship to feeding, was seldom projectile, and improved transiently after medical treatment. An occasional symptom-free interval of 24 hours was seen, unassociated with a change in therapeutic regimen. All infants had voracious appetites. Gain in weight was usually adequate up to several days after vomiting began. Loss of weight and character of the stools were consistent with the amount and duration of vomiting. The pyloric tumor was easily palpated through the thin abdominal wall. Gastric distention and visible peristalsis were observed late or not at all. Dehydration was not a significant finding. Mild alkalosis was consistently present.

DISCUSSION

The onset of vomiting in 3 cases was later than the expected average for full-term infants whose illnesses are usually diagnosed in the fourth to sixth week of life, after approximately 2 weeks of symptoms.[4-7] In another of our cases (No. 5), vomiting appeared 3 weeks after birth but progressed so slowly that it did not become notable until 1 month later. (Continuous medical supervision from birth and retrospective analysis would tend to designate an earlier onset of symptoms in our cases.) Kehl and Lange[1] have reported that 7 of 17 premature infants with pyloric stenosis began to vomit during the fifth week, in contrast to the authors' expectations of an earlier onset in the full-term infant. They did not comment

Table II. Characteristics of 5 premature infants with pyloric stenosis

Case	*Sex*	*Race*	*Weight at birth (grams)*	*Order of birth*
1	F	Caucasian	1,475 (3 pounds 4 ounces)	Second
2	F	Mexican	1,245 (2 pounds 12 ounces)	Third
3	F	Mexican	1,390 (3 pounds 1 ounce)	Seventh
4	F	Caucasian	1,280 (2 pounds 13 ounces)	Third
5	F	Negro	879 (1 pound 15 ounces)	First

Table III. Summary of clinical data of 5 premature infants with pyloric stenosis

Case	*Onset of vomiting (age in days)*	*Time of operation (age in days)*	*Per cent of weight loss (preoperative)*	*Complications (preoperative)*
1	35	73	6	Erythroblastosis
2	37	55	13	Pneumonia
3	24	33	5	None
4	31	42	10	None
5	21 (?80)*	88	4	Pneumonia

*Significant vomiting appeared at 80 days of age.

Table IV. Age at onset of pyloric stenosis in reported cases of premature infants*

Author	*Date*	*No. of infants*	*Weight at birth (grams)*	*Age at onset (weeks)*
Gallagher[8]	1937	1	1,600	4
Henderson and associates[9]	1952	3	1,468 (twin)	5
			1,772	1½
			1,928	3½
Josephs and Hendry[10]	1950	1	1,900	2
Kaiser[11]	1924	1	1,700	Since birth
Kehl and Lange[1]	1957	17	Not stated	5 for 7 infants
Sheldon[12]	1938	1	1,814 (twin)	Since birth
Steen[13]	1930	1	2,268	2
Vickers and Conrad[14]	1950	1	1,814	4
Weeks and Brooks[15]	1925	1	1,800	4
Williams[16]	1942	1	1,638	5
Wilson	Current paper	5	1,475	5
			1,245	5
			1,390	3½
			1,280	4½
			879	3

*Premature infants are those who weigh 2,500 grams or less at birth, with the arbitrary exclusion of a twin weighing over 2,000 grams.

upon other distinctions of the illness in the premature infant. A later onset of pyloric stenosis in prematurely born infants, if verified, would suggest that either pyloric stenosis is dependent on a certain degree of maturity or that different postnatal influences operate in the 2 groups of infants. The reported ages at the onset of pyloric stenosis in premature infants, however, vary considerably (Table IV).

The first appearance or a notable increase in vomiting a few days after the change from gavage to nipple feeding was an interesting observation in 4 cases. An increase in pyloric peristalsis and resulting edema might have occurred at that time. The tendency of a change in feeding to be associated with symptoms might have been a coincidence or merely an indication of another relationship, such as nipple feeding and infant size.

Henderson and associates[9] reported 3 cases of pyloric stenosis in premature infants in whom anorexia appeared shortly after vomiting began. Our infants, on the contrary, ate eagerly. Anorexia was noted late in Case 1, in whom the pyloric obstruction had progressed to the stage of inanition and starvation stools. Other observations of Henderson and associates[9] were similar to ours: vomiting was not usually projectile, gastric waves were of no particular diagnostic aid, and the pyloric tumor was easily felt.

Consideration of the diagnostic difficulties was particularly instructive. Vomiting, although recognized as significant, was frequently thought to be due to a nonsurgical condition. Vomiting in Case 1 was interpreted as a nonspecific symptom in a premature infant who was recovering from erythroblastosis. Vomiting in Cases 2 and 5 was thought to be secondary to pneumonia. The small weight at birth of infant No. 5 (879 grams), in itself associated with an infant fatality rate of almost 100 per cent, undoubtedly contributed to the attention on complications of prematurity. Nonforcible vomiting in all instances tended to deemphasize the possibility of pyloric stenosis.

Temporary improvement following feeding changes or medication delayed the diagnosis. In this regard, Still's[17] comments made in 1923 are pertinent: ". . . Infants with peristalsis and tumor, proved subsequently by operation to be due to hypertrophy of the pylorus, have had intervals of 2 or 3 days, sometimes even as long as 5 days, when the vomiting has temporarily ceased entirely and food passes through the pylorus normally.

. . . In this connection also I would mention another feature which is usual in this disorder, though not peculiar to it . . . that each change of food is apt to be followed by lessening or cessation of the vomiting for 24 to 48 hours, after which the vomiting becomes as troublesome as before. This repeated temporary improvement is another source of error in diagnosis."

Radiologic study of the upper gastrointestinal tract occasionally demonstrated the pyloric obstruction, but at a time when the diagnosis was readily apparent clinically. In 3 instances a pyloric mass had been felt while the concurrent x-rays were interpreted as "hypodynamic upper gastrointestinal tract with normal architecture" (No. 3); "normal" and "a 3-hour gastric retention" (No. 4); and "moderate gastric distention" (No. 5). Since varying degrees of gastric retention and hypoactive peristalsis are found in the premature infant, expectation of a corroborating radiologic study delays operation and exposes an infant to unnecessary radiation. Infantile pyloric stenosis in any case is a clinical diagnosis.

The laboratory finding of mild alkalosis might be expected to alert clinicians to the possibility of a high gastrointestinal obstruction since alkalosis is relatively uncommon in premature infants with vomiting secondary to a systemic illness.

The following conclusions seem warranted. Vomiting without bile, weight loss or failure to gain, and a voracious appetite in the premature infant less than 3 months of age are likely to represent pyloric stenosis. The diagnosis may be made definitely after palpation of the pyloric tumor. Particularly in the case of the premature infant who has been in the hospital since birth, the diagnosis should be made prior to deterioration of the infant's health. A prompt operation, with a reasonable time for fluid and electrolyte correction, may be followed by as prompt a recovery period as in full-term infants. Delay in the healing of a wound, found in 1 of our cases, may occur more frequently in the premature infant who has had an abdominal operation.

SUMMARY

Pyloric stenosis in the premature infant presents a deceptively milder clinical picture than it does in a full-term infant. Because of the attention given to possible complications of prematurity, the diagnosis may not be considered until it is too late. Intermittent regurgitation, lack of forcible vomiting, and temporary improvement following medical treatment may also obscure the diagnosis. The clinician is likely to expect the dramatic symptoms of projectile vomiting, loss of weight, and absence of stools that are frequently seen in the infant brought from home. Reliance on diagnostic radiologic studies may delay an operation unnecessarily.

A premature infant, 3 months of age or less who vomits gastric contents, fails to gain weight, and is constantly hungry, is likely to have pyloric stenosis. Palpation of the pyloric tumor is certain evidence of the diagnosis.

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Ristocetin, a laboratory and clinical evaluation in children

Charles P. Dries, M.D., and Richard Koch, M.D.*

LOS ANGELES, CALIF.

THE INCREASING importance of serious penicillin-resistant staphylococcal infections has created a need for more effective antibacterial agents. Ristocetin,† one of the newer antibiotics with bactericidal activity, is effective against staphylococci as well as other gram-positive organisms.[1, 2, 3]

The purpose of this study was to extend our previous observations regarding optimal dosage of this antibiotic and to evaluate its clinical usage.[4]

MATERIAL AND METHOD

Forty-nine hospitalized children were selected in order to make determinations of serum and cerebrospinal fluid ristocetin levels. These children were chosen for this study because they did not have any metabolic or renal disease. They ranged in age from 2 days to 15 years. Ristocetin was administered in a dosage of 12.5 or 25 mg. per kilogram by the intramuscular or intravenous route. The intravenous preparation was administered intramuscularly to 20 subjects in a ratio of 1 mg. of hydrocortisone per 100 mg. of the antibiotic. Twelve also had cerebrospinal fluid level determinations following administration of the drug.

Blood samples were collected by venipuncture, allowed to clot, centrifuged, and the serum stored in a freezer at –17° C. until sufficient numbers were collected for determination of ristocetin content. The specimens were then assayed with *Streptococcus pyogenes* as the test organism and with the use of a standard serial twofold dilution method.*

Fifty-two hospitalized patients treated therapeutically with ristocetin were considered in this report for clinical evaluation, and 55 were considered for toxicity data.

SERUM AND CEREBROSPINAL FLUID DATA

Thirty-three blood samples were obtained from 8 patients from 2 to 12 hours after rapid intravenous administration of 12.5 mg. per kilogram of ristocetin. As may be seen in Fig. 1, the ristocetin serum level varied from 1.3 to 10.6 μg per milliliter 2 hours after administration and then gradually decreased to less than 0.7 μg per milliliter by the end of 12 hours.

From the Department of Pediatrics of the University of Southern California and the Childrens Hospital of Los Angeles, Calif.

Supported by a grant from Abbott Laboratories.

**Address, Childrens Hospital Society of Los Angeles, 4614 Sunset Boulevard, Los Angeles 27, Calif.*

†*Spontin is the trade name of Abbott Laboratories for ristocetin.*

*Serum assays were performed by Bio-Science Laboratories, Los Angeles, Calif.

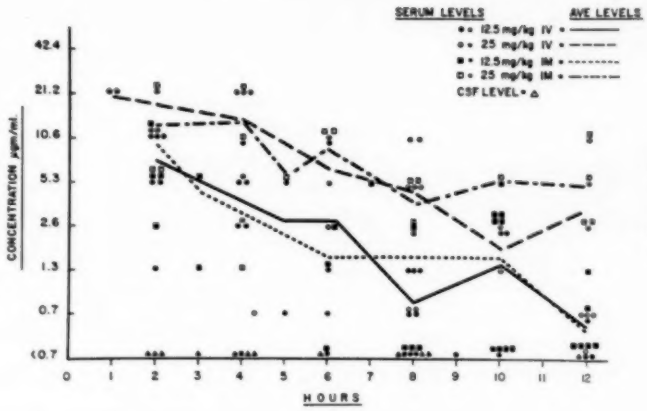

Fig. 1. Ristocetin serum and cerebrospinal fluid content following a single intravenous or intramuscular injection of 12.5 or 25 mg. per kilogram.

Thirty-one blood samples were obtained from 13 patients in a like manner after intravenous administration of 25 mg. per kilogram. An average level of approximately 18 μg per milliliter of ristocetin was maintained for 4 hours following injection and then gradually tapered off to an average of 2.5 μg per milliliter at the end of the 12-hour observation period.

In addition, single blood samples were obtained after 24 hours of continuous intravenous administration from 6 patients who received 50 mg. per kilogram per day. The serum content remained between 2.6 and 21.1 μg per milliliter during the infusion.

Twenty-seven blood samples were also obtained from 14 subjects following intramuscular injection of 12.5 mg. per kilogram. Serum levels ranged from 2.6 to 10.6 μg per milliliter for an average of 5.3 at 2 hours and gradually decreased to less than 0.7 μg per milliliter 12 hours after administration.

Seventeen samples of blood were obtained from 8 subjects after intramuscular doses of 25 mg. per kilogram. As with intravenous administration, this dosage again produced excellent serum levels throughout the 12-hour observation period. Levels as high as 5.3 μg per milliliter were found even as long as 12 hours following injection. The intramuscular route produced serum levels of ristocetin comparable to those obtained following intravenous administration.

Simultaneous serum and cerebrospinal fluid ristocetin determinations were performed on 12 patients without meningitis and on 1 patient with meningitis. The spinal fluid content of ristocetin remained less than 0.7 μg per milliliter, regardless of the dosage or route of administration.

CLINICAL RESULTS

Fifty-two patients with various types of pyogenic infections were treated with ristocetin. Forty-one of these had infections due to hemolytic *Staphylococcus aureus,* coagulase positive. Of the latter, 32 were treated with ristocetin alone; the other 9 received additional antibiotic therapy because of the severity of their illness.

The clinical results of the various types of staphylococcal infections treated with ristocetin alone are shown in Table I. In general, the clinical response was prompt; however, 5 patients failed to improve and 1 died. The other 11 children had infections due to the following: 5, pneumococcus; 3, streptococcus; 1, *Hemophilus influenzae* type B; 1, aerogenes; and 1, Proteus. Ten of these 11 patients responded promptly to ristocetin therapy; 1 patient with pneumococcal pneumonia and empyema (Fig. 2) failed to improve. Three other patients in whom no pathogenic organism was isolated were excluded from the clinical results but are included in the toxicity data. In the 52 patients treated

Table I. Clinical results in 32 patients with staphylococcal infections treated with ristocetin alone

Number	Diagnosis	Clinical results		
		Cure	Unimproved	Died
1	Septicemia	1	–	–
1	Subacute bacterial endocarditis	–	1	–
2	Meningitis	–	2	–
9	Cellulitis and/or abscess	9	–	–
2	Pneumonia with empyema	1	1	–
5	Pneumonia without empyema	5	0	–
12	Respiratory infection other than pneumonia	10	1	1*
	Total	26	5	1

*This child had associated fibrocystic disease of the pancreas.

with ristocetin, there appeared to be a relationship between dosage and clinical response (Table II). Of the 33 patients treated with 25 mg. per kilogram daily, 7, or approximately 21 per cent, failed to improve and 1 died. The latter was an 11-year-old patient with fibrocystic disease of the pancreas and staphylococcal bronchiectasis who died 36 hours after initiation of ristocetin therapy. Of 19 patients treated with 50 mg. per kilogram daily, only 2 patients, both with staphylococcal pneumonia and empyema, failed to respond adequately. The clinical course of a patient who initially failed to respond to a 25 mg. per kilogram dosage of ristocetin referred to in Table II is outlined in Fig. 3.* This 11-year-old girl developed bacterial endocarditis due to hemolytic *Staph. aureus.* She failed to respond to erythromycin, chloramphenicol, bacitracin, tetracycline, vancomycin, and ristocetin. She did, however, show a good clinical response to a higher dosage (75 mg. per kilogram) of ristocetin which was maintained for 35 days. She has remained free of infection since, although she is chronically ill with periarteritis nodosa.

A dose of 25 mg. per kilogram daily has been previously recommended for adults.[5-8] Our data suggest that this dosage is inadequate for children. The following 2 case histories are presented in detail in order to demonstrate the need for higher dosage when children with serious infections are treated.

The clinical course of a patient with staphylococcal meningitis who failed to respond to ristocetin therapy is illustrated in Fig. 4. This 5-year-old white boy initially improved rapidly on chloramphenicol and ristocetin therapy. Five days later the chloramphenical was discontinued and he was maintained on ristocetin alone. Two days later, despite ristocetin therapy, there was a recrudescence of symptoms. The cerebrospinal fluid ristocetin content at the time of

*Previously reported case.[4]

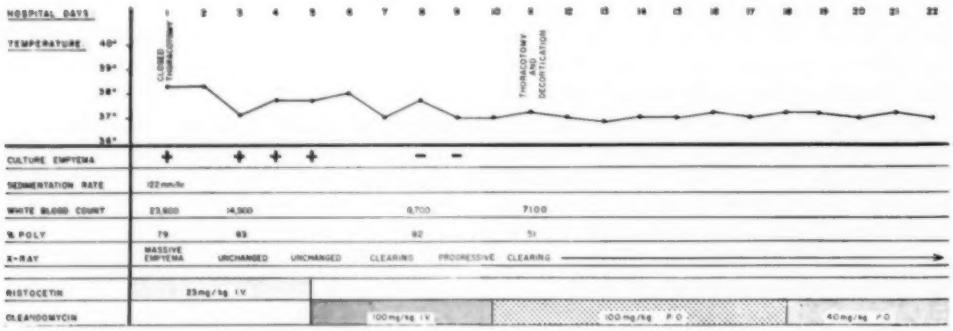

Fig. 2. Clinical course of a 14-year-old white girl (J. B. 150278) with pneumonia and massive left empyema due to pneumococcus.

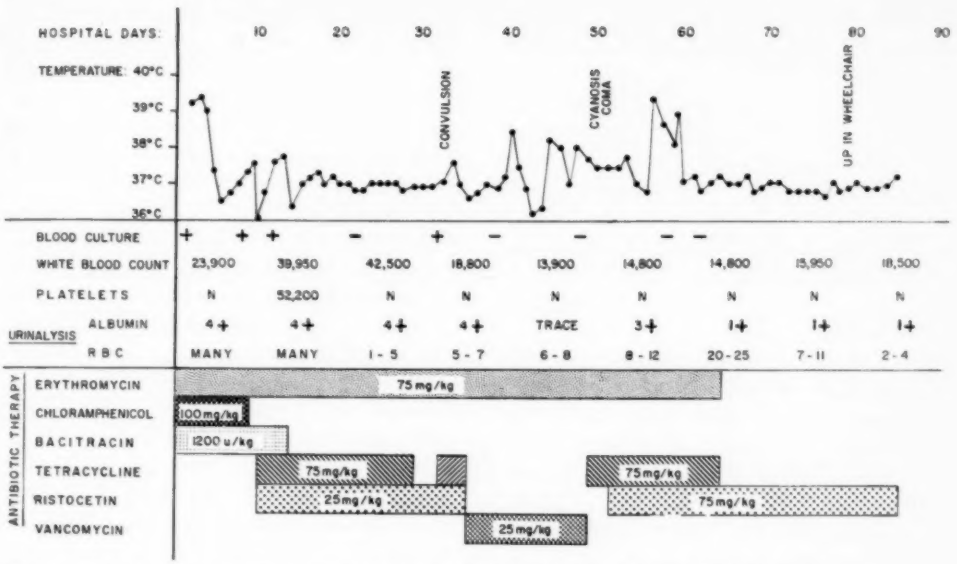

Fig. 3. Clinical course of an 11-year-old girl (147284) with bacterial endocarditis due to hemolytic *Staph. aureus* resistant to penicillin. (From Dries, Asay, and Koch: Antibiotics Annual 1958-1959, Medical Encyclopedia, Inc., p. 430.)

relapse was less than 0.7 μg per milliliter and the serum level was only 2.3 μg per milliliter. These values suggest that ristocetin at this dosage does not enter the cerebrospinal fluid in adequate therapeutic amounts.

Another patient with pneumococcal pneumonia and empyema also failed to respond to ristocetin therapy. Her clinical course is outlined in Fig. 2. This 14-year-old youngster had massive empyema from which pneumococcus was isolated on culture four times over a 5-day period despite therapy with intravenous ristocetin at 25 mg. per kilogram per day. Empyema fluid did not demonstrate measurable levels of ristocetin content. Oleandomycin was substituted for ristocetin on the fifth hospital day. Subsequently, the cultures from the empyema remained sterile; she became afebrile and made an uneventful recovery.

TOXICITY

Thirty-seven (67 per cent) of 55 patients treated with ristocetin showed no evidence of toxicity. The individual reactions are listed in Table III. Generally, they were not serious. An eosinophilia of 4 to 8 per cent was the most frequent aberration noted in the peripheral blood count. Leukopenia occurred in 4 patients. This has been previously noted by others.[5-9] After discontinuance of ristocetin, the blood count returned to normal within 48 to 72 hours.

As the dosage of ristocetin was increased, there was a greater incidence of toxicity (Table IV). There was a similar relationship between toxicity and total dosage. Three of 4 patients who received 10 Gm. or more of ristocetin each had toxic reactions, such as rash, eosinophilia, and thrombophlebitis. Evidence of local tissue reaction at the site of injection was sought in 58 children. Of the first 4 patients receiving ristocetin intramuscularly, 2 had moderate reactions consisting of erythema, tenderness, and induration. Thereafter, hydrocortisone, 1 mg. per 100 mg. of ristocetin, was added to the intramuscular solution for the next 54 patients. Only 2 of this latter group developed induration and erythema, although 6 were

Table II. The relationship of dose to clinical response with ristocetin therapy in 52 cases

Dose (mg./Kg./day)	*Cure*	*Clinical result unimproved*	*Death*
25	25	7	1
50	17	2	–
75	2*	–	–
Total	44	9	1

*Responded to 75 mg. per kilogram per day but not to 25 or 50 mg. per kilogram per day.

Table III. Clinical toxicity related to ristocetin therapy in 55 patients

Toxicity	*No. of cases*	*Per cent*
None	37	67.3
Eosinophila	8	14.5
Skin rash	4	7.3
Leukopenia	4	7.3
Local reaction at injection sites*	4	7.3
Thrombophlebitis†	1	1.8
Sterile abscess	1	1.8

*Two patients received ristocetin intramuscularly without cortisone.

†Dosage at 75 mg. per kilogram per day.

Table IV. Clinical toxicity related to dosage of ristocetin

No. of patients	*Dose (mg./Kg./day)*	*No. of patients with toxic reactions*	*Per cent toxicity*
35	25	6	17.3
20	50	7	35
2*	75	2	100

*Had previously received ristocetin in lower dosage.

treated for more than 16 days with injections every 8 to 12 hours. One patient developed a sterile abscess which responded to surgical drainage. The abscess was first noted 2 weeks after the discontinuation of ristocetin therapy.

DISCUSSION

Hwang and co-workers[11] demonstrated that there was a gradually decreasing plasma content after intravenous administration of ristocetin to dogs. It was shown by Grundy and associates[12] that in rabbits ristocetin was found in the blood for only 3 hours after intravenous administration but up to 8 hours after intramuscular administration. The data reported herein demonstrate that the serum ristocetin content is measurable for 8 hours following intravenous administration of 12.5 mg. per kilogram and for 12 hours after a dose of 25 mg. per kilogram. The serum content of ristocetin in our patients, 2.6 μg per milliliter or greater, even after 12 hours with 25 mg. per kilogram intramuscularly, is comparable to the results in rabbits.[11]

Romansky and co-workers[2] found that ristocetin was maximally active against the pneumococcus; all of the 74 strains studied by them were sensitive to serum levels of 3 μg per milliliter or less. Seventy-five per cent of 90 strains of streptococci were sensitive to 5.0 μg per milliliter or less, and all 35 strains of hemolytic *Staph. aureus* tested were sensitive to 5 μg per milliliter or less. These values are similar to the serum levels of ristocetin obtained in patients who received a dosage of 50 mg. per kilogram per day. The serum level data and the number of therapeutic failures with administration of 25 mg. per kilogram per day (Table II) suggest that this dosage is not adequate for children.

As noted in Table I, an over-all favorable response to ristocetin therapy occurred in 81 per cent of all patients treated. It is our impression that therapeutic failure was either on the basis of inadequate dosage or perhaps due to the poor diffusibility of ristocetin across tissue barriers resulting from its large molecular size.

All clinical evidence of toxicity summarized in Table III subsided promptly with discontinuance of the antibiotic. As reported elsewhere,[13] there seemed to be a relationship between the dosage and the incidence of toxic reactions (Table IV). Rash and leukopenia were indications for discontinuance of therapy, although simultaneous bone marrow studies were normal in 2 such patients. Eosinophilia was not considered a contraindication to continued therapy. Thrombocytopenia was not observed in this study.

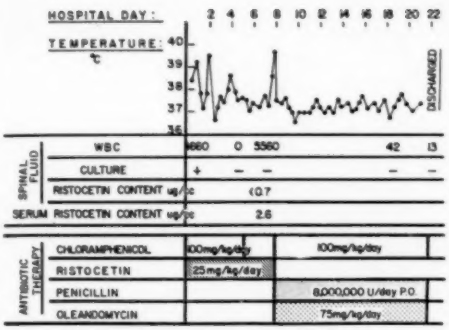

Fig. 4. Clinical course of a 5-year-old boy (M. S. 161082) with staphylococcal meningitis with relapse while on ristocetin therapy alone.

The use of steroids to minimize local tissue reactions to intramuscular injection of ristocetin was suggested by the work of Krugman and Ebin[14] who first utilized prednisolone with intramuscular benzathine penicillin G. The use of hydrocortisone appeared to decrease markedly the problem of tissue intolerance due to intramuscular administration.

Older children complained of pain at the site of intramuscular injection; therefore this route of administration is recommended primarily for treating infants in whom the intravenous route is technically difficult to maintain.

As found by Hwang and associates[11] in their work on dogs and by Kanner,[15] there was little, if any, ristocetin found in cerebrospinal fluid after parenteral administration. In our series of 13 children, ristocetin did not appear in measurable quantities in the cerebrospinal fluid, although in 1 case the meninges were inflamed.

SUMMARY

1. The recommended dose of ristocetin for children is 25 mg. per kilogram every 12 hours. Adequate serum levels are produced by this dosage by either the intravenous or intramuscular route.

2. The intravenous preparation of ristocetin can be administered safely intramuscularly if 1 mg. of hydrocortisone per 100 mg. of ristocetin is added to the diluent. This route is particularly useful for treating infants.

3. Ristocetin does not diffuse into the cerebrospinal fluid in significant amounts.

4. A cure rate of 87 per cent in 52 patients treated with ristocetin intravenously and/or intramuscularly was noted. The majority of therapeutic failures occurred in patients treated with a dose of 25 mg. per kilogram per day.

5. Sixty-seven per cent of our patients tolerated ristocetin therapy without difficulty. Mild eosinophilia, the most common peripheral blood change noted, occurred in 15 per cent of the patients. Leukopenia with neutropenia occurred in only 4 patients. No cases of thrombocytopenia were observed.

6. It is our impression that ristocetin is an effective antibiotic for treatment of serious staphylococcal infections. It is not recommended for therapy of meningeal infections, however.

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FROM NATIONAL CLEARINGHOUSE FOR POISON CONTROL CENTERS OF THE U. S. PUBLIC HEALTH SERVICE, DECEMBER, 1959, COMMUNICATION TO POISON CONTROL CENTERS.

Birth weights of infants of toxemic mothers

Pierre H. Beaudry, M.D.,* and James M. Sutherland, M.D.**

CINCINNATI, OHIO

THAT INFANTS of toxemic mothers are small at birth is frequently asserted. There is some support for this concept in the medical literature.[1, 2] This feeling is not universal, however. For instance, Brasch[3] concluded that infants of toxemic mothers were not significantly smaller than control infants. More recently, Baird, Thomson, and Billewicz[4] concluded that low birth weight was not generally associated with pre-eclampsia, although there was a tendency for low birth weight to occur when the eclampsia was severe and delivery took place before term.

In consequence of a review of the autopsy findings in infants of toxemic women, preliminary observations suggested that the birth weights were not significantly different from those of the control infants. Because any comparison of the birth weights of two groups of infants is more valuable if length of gestation is considered, a correlation of birth weight and length of gestation was undertaken in infants of "toxemic" and "normal" mothers.

From the Department of Obstetrics and the Department of Pediatrics, University of Cincinnati College of Medicine, the Laboratory for the Study of Infant and Maternal Health, and the Children's Hospital Research Foundation, Cincinnati, Ohio.

**Research Fellow, supported by Grant RG 5099, the Department of Health, Education and Welfare, Public Health Service. Present address, Montreal Children's Hospital.*

***Address, The Children's Hospital Research Foundation, Elland Avenue and Bethesda, Cincinnati 29, Ohio.*

DEFINITIONS

The disagreements about terminology and definitions in the field of toxemia of pregnancy can be understood when one considers the lack of knowledge of its causes or even its pathologic physiology. Both "toxemia" and "pre-eclampsia" are widely used terms that do not have any precise, generally accepted meaning. Criteria for diagnosis of pre-eclampsia vary.[5, 6] The criteria used here are those of the Obstetric Service of the Cincinnati General Hospital. Women are *pre-eclamptic* who: (1) have a blood pressure of 140/90 mm. Hg or more or (2) have a rise of more than 30/15 mm. Hg above their pre-existing, well-documented level. Two elevated readings, not determined during uterine contractions and preferably taken by different observers, are required before the diagnosis of pre-eclampsia is accepted. The occurrence of edema or albuminuria is not essential to the diagnosis of pre-eclampsia, even though one or the other or both is usually present. Edema and/or albuminuria alone are not classified under the diagnosis of toxemia. Pre-eclamptic individuals are not subdivided according to the mildness or the severity of the disease. Those with essential

Table I. Average birth weight of infants at Cincinnati General Hospital during 1956*

	Number of cases	*Mean birth weight (grams)*	*Standard deviation (grams)*
White			
Males	711	3,201	696
Females	675	3,076	637
Males and females	1,386	3,140	670
Non-white			
Males	1,352	3,096	611
Females	1,330	2,976	442
Males and females	2,682	3,037	537
White and non-white			
Males	2,063	3,132	643
Females	2,005	3,010	518
Males and females	4,068	3,072	588

*Including all single liveborn infants weighing 500 grams and above.

Table II. Average birth weight of infants* of toxemic† mothers

	Number of cases	*Mean birth weight (grams)*	*Standard deviation (grams)*
White			
Males	55	3,298	± 662
Females	52	3,254	± 635
Males and females	107	3,277	± 650
Non-white			
Males	154	3,160	± 573
Females	157	2,973	± 562
Males and females	311	3,065	± 575
White and non-white			
Males	209	3,196	± 601
Females	209	3,043	± 594
Males and females	418	3,117	± 603

*Including all single liveborn infants weighing 500 grams and above.

†Including all degrees of toxemia.

hypertension are analyzed separately in this paper.

The criteria for the diagnosis of eclampsia are uniform and readily recognized. Mothers who have had seizures before, during, or after delivery and in whom other convulsive disorders are excluded, are considered to have eclampsia.

Toxemia includes patients with pre-eclampsia, with and without essential hypertension, and patients with eclampsia.

MATERIAL AND METHOD

The individuals studied are from the Obstetric Service of the Cincinnati General Hospital which cares for the indigent population of Cincinnati. Stillborn infants, infants of less than 500 grams, and infants who were born of multiple pregnancies are excluded in the present study. Birth weights of the 4,068 newborn infants in 1956 were tabulated and used as control data. They are referred to as normal infants. In addition, the gestation periods of 930 similar babies, born consecutively in 1958, were recorded. These two groups are comparable with respect to birth weight, race, and sex. This second group of normal infants will be used when comparing birth weight of normal and toxemic infants at different gestational ages.

Because the proportion of Negro to white is 2 to 1, these two groups are separated in the presentation of our data, for the birth weight and gestational periods of Negroes and whites differ significantly.[7-10] Whether this difference is of racial, socioeconomic, or other origin is debatable.[8] Since Negroes and whites appear in the two groups of toxemic and normal infants in equal proportions, however, the discussion is limited to the total data, and the groups are treated as homogeneous. The data are also subdivided according to sex, but again the discussion is limited to the total data.

There were 418 liveborn infants of mothers classified as toxemic at the Cincinnati General Hospital in 1956; 27 had associated essential hypertension and 6 had eclampsia.

Eclampsia might be expected to be associated most consistently and to a more severe degree with any fetal disturbances resulting from maternal toxemia. Therefore, the normal and toxemic infants are also compared with the 87 infants of eclamptic mothers born from 1937 to 1957.

RESULTS

The mean birth weight of the 4,068 normal infants (Table I) born in 1956 is 3,072 grams (S.D., 588 grams). The 418 toxemic infants born in the same year (Table II) had a mean birth weight of 3,117 grams

(S.D., 603 grams). The weight of the toxemic group is not lighter than the control group; on the contrary they outweigh the normal group by 45 grams. The difference is small, however, and is not statistically significant; p is 0.2 by Student's "t" test.[11] The fact that the data of the heavier toxemic group are included in the calculation of the mean birth weight of the control group minimizes the difference and serves to emphasize that the toxemic infants are not smaller than the normal infants.

The differences in the birth weights between each of the subgroups of normal and toxemic infants were also analyzed with Student's "t" test (Table III). The difference was not significant in any of the comparisons.

It is interesting to note that the data in Table I confirm what has been shown previously in this hospital,[7] that normal male infants are larger than normal females, and that normal white infants are larger than normal non-white infants.

Gestation age was calculated from the date of onset of the last menstrual period. This information was available for 346 of the 418 toxemic infants. The mean birth weight for each day of gestation was calculated. These same calculations were carried out for the 930 normal infants in 1958.* Members of this control group did not differ significantly in mean birth weight from the control group in 1956 or from the toxemic infants in 1956.

The normal growth of the fetus and infant from conception through the first year of extrauterine life follows the curve characteristic of growth of human populations. This is a logistic curve described by the equation $y - d = \frac{K}{1 + Ce^{rt}}$ [12] where K and I are parallel and asymptotic to the curve. The lower asymptote, d, is assumed to be equal to 0, the approximate weight of the fetus at the time of conception. The equation used was thereby simplified to $y = \frac{K}{1 + Ce^{rt}}$.* The value chosen for the upper asymptote, K, which best fitted our data, was 10 kilograms. The symmetric, logistic curve representing the toxemic infants in 1956 is expressed by $y = \frac{10}{1 + 2.642e - 0.00813t}$. The curve representing the 1958 normal infants is $y = \frac{10}{1 + 2.63e - 0.005t}$. These equations are graphically expressed in Fig. 1 with the mean birth weights for each day of gestation. The curves intersect at 251.28 days of gestation, the toxemic infants being slightly lighter if birth occurs before that time and heavier if birth occurs after that time.

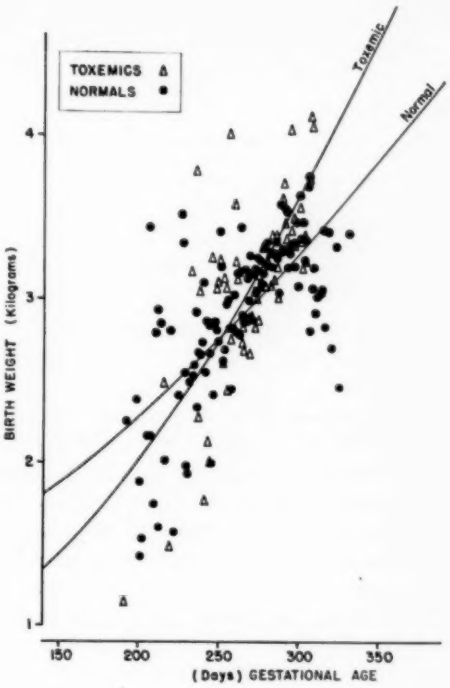

Fig. 1.

Those infants whose mother's toxemia was complicated by essential hypertension had a

*Mean birth weight for each day of gestation has been tabulated for the 930 normal infants (1956), 346 toxemic infants (1958), and 59 infants of eclamptic mothers (1937 to 1957). More detailed tabular material has been deposited as Document No. 6105 with the ADI Auxiliary Publications Project, Photoduplication Service, Library of Congress, Washington 25, D. C. A copy may be secured by citing the document number and by remitting $1.25 for photoprints or $1.25 for 35 mm. microfilm. Advance payment is required. Make checks or money orders payable to Chief, Photoduplication Service, Library of Congress.

*y = birth weight.
K, C, and r are constants.[12]

Table III. Difference in birth weight between normal and toxemic infants

	Difference in birth weight (toxemic minus normal infants (grams)	*t*	*Probability (p) of occurrence by chance of a difference as great as that observed*
White males	96	1.04	0.3
White females	178	1.95	0.05
White males and females	136	2.09	0.05
Non-white males	63	1.29	0.2
Non-white females	−3	0.07	> 0.9
Non-white males and females	28	0.84	0.4
White and non-white males	63	1.45	< 0.2, > 0.1
White and non-white females	33	0.78	< 0.5, > 0.4
White and non-white males and females	44	1.45	< 0.2, > 0.1

mean birth weight of 3,065 grams (S.D., 522 grams) which is close to the weight of the normal infants and not significantly different from those of the other toxemic infants. The mean birth weight of 89 infants of eclamptic mothers reviewed was 2,858 grams (S.D., 669 grams). The difference between the eclamptic and the normal individuals is significant at the 1.5 per cent level. The importance of this finding is difficult to assess, for over the years the racial proportion of the hospital population has changed, and unrecognized changes in the nutritional, socioeconomic, and medical status of the patients may have occurred.

The infants of toxemic mothers at the Cincinnati General Hospital in 1956 did not differ significantly in mean birth weight from the control infants or was there any difference between the two groups when the weight at birth at different gestational periods was examined. The toxemic infants were similar to those in other recent series[13] when fetal loss and neonatal mortality were compared. The findings reported here apparently cannot be explained by differences in severity of toxemia or variations in the criteria used for the diagnosis.

DISCUSSION

Little has been published on the pathologic[3, 14] or physiologic[3, 15] aspects of infants of toxemic mothers. This is unusual, for fetal loss and neonatal mortality are higher in these infants.[1, 2, 3, 13, 16, 17] Lack of interest is not the explanation for the paucity of information. Our own search for pathologic and physiologic variations from the normal has been disappointing. The absence of distinctive pathologic findings[3, 13] probably accounts for the lack of published information.

The dilemma accounts for an increased mortality rate unassociated with distinctive pathologic stigmas and a normal birth weight in those infants who are born alive. The great majority, presumably of normal nutritional state, survive and escape serious physiologic setback.[3]

Usually the symptoms of toxemia are of short duration. The noxious effects on the offspring, if related to the maternal symptoms, should also be of short duration. Death might result without obvious changes in nutritional state or obvious pathologic findings. It is probable that the demonstration of the effect of toxemia on the fetus awaits the advent of more efficient techniques for demonstrating early changes in tissues following injury, such as those described in the central nervous system by McAdams, Kobayashi, and Landing.[18]

Kloosterman and Huidekoper[19] have shown that the placenta is not an organ with great reserve. On the contrary, their excellent study demonstrates that the reserve capacity of the placenta is small. If this is true, and if decreased uterine and placental circulation are factors in the causation of toxemia,[20, 21, 22] it is probable that severe fetal damage, though unrecognized, is responsible for both the fetal and neonatal mortality. The fact that the symptoms of

toxemia are usually rapidly and efficiently controlled might explain why the offspring, while often fatally injured, may not be stunted in growth. Decrease in growth is not an essential corollary to injury in utero, as has been implied by others,[21] even though it might frequently be associated with death in utero.[1] The placental weight–birth weight ratio of the infants of toxemic mothers has been shown to be normal.[4, 19] Weight cannot, however, be taken as a satisfactory criterion of functional integrity, and until finer techniques for assessing placental function are devised, there is no way of measuring the extent of placental injury and its possible role in the pathogenesis of toxemia.

SUMMARY

A comparative study of the birth weights of infants of toxemic mothers and of nontoxemic control infants was conducted at the Cincinnati General Hospital. The data were analyzed, and weight at birth and calculated gestational age at time of delivery were correlated. Contrary to what is generally believed, and has often been reported, the birth weights of the toxemic group were not lower than those of the control group. Indeed, the toxemic infants were larger than the control infants, though the weight difference was not statistically significant. The comparison of the correlation between birth weight and gestational age emphasized the fact that the two groups did not differ from one another.

The authors wish to acknowledge the invaluable assistance of Mrs. Virginia Lohre.

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Early recognition of infantile autism

S. Robert Lewis, M.D.,* and Shirley Van Ferney, M.D.

PRINCETON, N. J.

IN 1944 Kanner[1] described a clinical syndrome, early infantile autism, which he has come to regard as the earliest form of schizophrenia. The syndrome is characterized by inability to relate to persons in a normal fashion, muteness or other abnormalities of speech, an obsessive insistence on sameness, as, for example, in activities such as feeding and bathing and in environmental situations such as arrangement of toys and furniture, and a tendency to react with a paniclike state should any change occur.

The condition is usually recognized at 3 to 4 years of age. In the child described here, arresting changes in behavior were noted during the early months of life. This, to our knowledge, is the youngest child ever reported to have infantile autism.

CASE HISTORY

S. B., a girl, was born at term following a normal vertex delivery. For the first 2 weeks of life she was cared for by a nurse, but thereafter the mother took over her care. During the first 4 months her appetite was voracious. At 7 weeks she weighed 13 pounds, a gain of 5 pounds.

At 3 months casts were placed on both feet for treatment of mild metatarsus adductus. They were removed after 7 weeks, the deformity apparently corrected.

**Address, 253 Witherspoon Street, Princeton, N. J.*

Her motor development was somewhat advanced: she rolled over at 3 months, sat at 6 months, stood at 6½ months with support, and walked at 10 to 12 months. The manipulation of objects was always good. The tendon reflexes were active. The pupillary reflexes were normal. The Moro embrace reflex disappeared by 2 to 3 months and the tonic neck reflexes by 3 months.

She was described by her mother as "fussy and colicky" for the first 3 to 4 months. She did not "like being held," would not smile, and never seemed to relax in her mother's arms. At about 4 months of age she began to stare intently for hours at a time at her hand or at an object held before her eyes. Her facies seemed blank, and responses were difficult to elicit. She would not focus her eyes on the examiner or on her parents.

At 5 months of age she smiled only rarely. She constantly held her head to the right when she was held or propped, and she seldom cried. When picked up she would arch herself away from the holder. For a time the mother felt certain that vision was impaired because the infant refused to look at her. However, the baby did follow light and did reach for objects. An ophthalmologic examination, including funduscopy, at 6 months of age was normal.

At 6 months of age she was admitted to the hospital for treatment of otitis media

and for further observation. The nurses were instructed to give her as much attention and affection as possible which they did willingly because they were alerted to the baby's difficulty and, also, because she was a most appealing child.

A complete blood count on admission showed a white blood cell count of 20,000 per cubic millimeter with 60 per cent polymorphonuclear leukocytes and 40 per cent lymphocytes. The urinalysis was negative, including a test for phenylketonuria. Skull films were negative. A culture obtained at the time of myringotomy revealed diphtheroid and coliform organisms. The otitis responded well to antibiotic treatment and, in the opinion of the otolaryngologist, the baby's hearing was adequate.

A distinct change in behavior took place during the 8 days of hospitalization. Her expression brightened; she began to smile spontaneously and would reach out to the nurses to be held. This change, however, was not apparent during the mother's visits. On the basis of her developmental history and observed behavior, a diagnosis of early infantile autism was considered at this time (6 months of age).

Following the hospitalization she quickly regressed to staring at her hand and rocking for prolonged periods of time with the head banging and whirling. At this time the mother thought that nothing was wrong with the baby because she was so "good." She would sit quietly for hours without bothering anyone. However, at any change in routine or in familiar surroundings she would scream hysterically.

At 2 years of age the mother noted that when children her own age came to play, "she stood aside and watched intently for a while, then went off on her own." Toilet training was started at approximately 9 to 10 months. It was unsuccessful up to the present age of 2 years. Speech is nonexistent except for a few repetitive sounds. She still has a bottle at night which she fondles as much as she drinks from it, but it is provided as a means to get her to sleep. She feeds herself awkwardly but still ingests large quantities of food.

The patient is the third child in a family of four. The oldest, a boy 5½ years of age, is normal, although described by the parents as hyperactive and demanding; the second, a boy 3 years of age, is institutionalized with a diagnosis of mongolism; the youngest child, a girl 5 months of age, is apparently normal.

The father is a college graduate whose work takes him out of the home at regular intervals. He is compulsive and rigid and states that all situations can be met with accurate scheduling. He presents an attitude of aloofness toward his wife, children, and current family problems.

The mother is anxious, tense, and depressed. She had maintained a close, dependent relationship with her parents until the family moved shortly prior to the patient's birth. At present she is overwhelmed by the demands of the family situation and feels incapable of fulfilling their needs.

During the initial psychiatric examination at 2 years of age, the child's spontaneous behavior was observed. She ignored any overture to being held, played with, or comforted. She was absorbed with objects in the room, twirled the swivel chair, and fingered paper in the wastebasket and desk drawer. During the second and longer visit attempts were made to divert the child's preoccupation with herself and with objects. For example, instead of allowing her to finger, mouth, and visually examine the ball she was forced into active play. The ball was rolled to her with repeated encouragements to return it to the therapist. Initially the child accomplished this by handing it to her but gradually began the game of rolling the ball back and forth. Her response to the persistent verbal and physical stimulation was marked; she looked directly at the therapist and on several occasions laughed appropriately. The affect, while still remaining detached, brightened perceptibly. On reappearance of the mother she quickly resumed the rigid, stoiclike, withdrawn facies.

In spite of her inability to use language, the child, on psychological examination,

was found to be only slightly below the normal intellectual level of her age group.

DISCUSSION

The early recognition of certain alterations in emotional adjustment and maturation provided an opportunity to follow the evolution of the syndrome known as early infantile autism. The diagnosis is supported by the subsequent development of the typical syndrome by the age of 2 years.

An interesting feature of this case was a reversal of the abnormal behavior when the child was separated from the mother and given active stimulation. Possibly the outlook in these children may be improved if the behavioral changes are recognized early and the parents are alerted to the need of young children for warm, human relationships.

We wish to acknowledge the aid, support, and insight concerning this case given by Dr. Harry Bakwin.

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Spontaneous infection of cephalhematoma with recovery

M. Jacobson, M.D.,* H. B. Lander, M.D., and**

I. J. Spiegel, M.D.

CHICAGO, ILL.

CEPHALHEMATOMA has been considered a relatively innocuous condition of the newborn infant. As Sanford and Grulee[1] have pointed out, infection is an extremely rare complication of this condition. It is for that reason that we present the following case.

E. P., a full-term Filipino boy, was born Oct. 30, 1957, at Michael Reese Hospital. Delivery was by routine outlet forceps after a 24-hour labor. At 24 hours of age, a large cephalhematoma was noted over the left temporal occipital area. Otherwise the infant was in good health. He was discharged on Nov. 5, 1957, without any evidence of local or general infection. The cephalhematoma was not aspirated or otherwise traumatized. On Nov. 21, at 3 weeks of age, he developed a mild upper respiratory infection and was treated with Achromycin. The infant did well following therapy and was gaining weight properly without any further evidence of infection. On Dec. 9, at 5 weeks of age, the cephalhematoma was noted to be increased markedly in size and spontaneous drainage began at its medial aspect. There were no associated signs or symptoms of systemic infection. He was admitted to the Sarah Morris Hospital of Michael Reese Hospital on the same day.

During physical examination upon admission he was noted to be well developed and well nourished; pertinent physical findings were limited to the skull. There was a fluctuant swelling, measuring approximately 4 by 4 cm. which overlay part of the left occipital parietal area with a circumscribed conelike point at its medial-superior aspect. From this area a sanguinopurulent material was discharged. There were no accompanying enlarged nodes. Skull x-rays on admission (Fig. 1) revealed a large cephalhematoma over the left occipital parietal region, with elevation of the periosteum in the midline. Over the posterior portion of the parietal bone there was increased radiolucency, indicating either demineralization secondary to the infection or osteomyelitis.

Thirty cubic centimeters of sanguinopurulent material was aspirated by the neurosurgeon (I. J. S.) shortly after admission and the exudate was cultured. Large amounts of purulent discharge drained from the

From the Department of Pediatrics and the Department of Neurosurgery, Michael Reese Hospital, Chicago, Ill.

**Resident in Pediatrics.*

***Address, 622 West Diversey Parkway, Chicago 14, Ill.*

Fig. 1. X-ray on admission showing large, left occipital parietal cephalhematoma.

Fig. 2. X-ray 4 months later showing complete resolution.

wound. A pyramidal pressure dressing was applied.

LABORATORY FINDINGS

Hemoglobin level was 8.1 Gm., white blood cells, 20,600; segmented polymorphonuclear leukocytes, 32 per cent; nonsegmented, 5 per cent; lymphocytes, 55 per cent; and monocytes, 8 per cent. Urinalysis was negative. Blood culture showed no growth, and nose and throat culture revealed 5 per cent hemolytic staphylococcus and was coagulase positive. No pathogenic organism grew in the stool culture. Culture material aspirated from the cephalhematoma yielded *Paracolobactrum coliforme*. Although the stool cultures of the infant did not contain this organism, it was recovered in the stool cultures of the parents.

The child was treated initially with penicillin and streptomycin and subsequently received Chloromycetin and Gantrisin to which the organism was sensitive. Improvement was prompt and the infected hematoma decreased in size. The infant received 80 c.c. of whole blood because of moderate anemia. Repeated x-rays of the skull showed some decrease in the size of the cephalhematoma. The baby was discharged on Dec. 24, 1957. Office follow-up indicated that the infant was completely asymptomatic.

The last skull film (Fig. 2), taken on April 10, 1958, showed complete resolution of the cephalhematoma and no evidence of underlying periosteal or bone destruction. There was a localized area of bony sclerosis about the previously infected bone, but both inner and outer tables were clearly defined.

COMMENT

This newborn infant with cephalhematoma showed no evidence of local or general infection except for a mild upper respiratory infection 2 weeks prior to admission. The cephalhematoma became infected spontaneously. *Paracolobactrum coliforme* was isolated from the abscess and from the stool cultures of the parents. Following therapy, the infant recovered with-

out ever having had systemic manifestations, local complications, or residual bony defects.

Cohen and Miller[2] reported an instance of cephalhematoma in a newborn infant with secondary infection which terminated in meningitis. There was no history of trauma to, or attempted aspiration of, the hematoma. That infant died. *Pseudomonas pyocyanea* was recovered from the hematoma. A similar case was observed by Kendall and Woloshin.[3] They reported an incidence of 69 cases of cephalhematoma among 2,474 infants. Various complications of cephalhematoma were discussed, but no mention was made (in their series) of spontaneous secondary infection.

Ingram and Hamilton[4] reported 126 cases of cephalhematoma in 7,563 infants. They noted 4 typical instances of calcifying cephalhematoma in their group, but no spontaneous infection was observed.

Paracolon bacilli are atypical members of the coliform group. They ferment lactose slowly, irregularly, or not at all. Most members of the paracolon group comprise the normal intestinal flora of man and animals. When pathogenic, they are usually secondary invaders and are commonly found in infections of the genitourinary tract and occasionally in the gastrointestinal and bone marrow infections. To our knowledge, these organisms have not been reported as spontaneously invading cephalhematomas.

We assume that the infant had a mild bacteremia 2 weeks prior to admission which was manifested by an apparent upper respiratory infection. The organisms presumably became localized in the cephalhematoma at that time.

SUMMARY

A spontaneously infected cephalhematoma *(Paracolobactrum coliforme)* in a newborn infant with complete recovery is reported. The secondary infection was presumed to follow a bacteremia which was manifest as an upper respiratory infection and which occurred two weeks earlier.

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Mitigation of posterior choanal atresia by cleft palate

Frank W. Kiel, Captain, MC, USA*

FORT SAM HOUSTON, TEXAS

POSTERIOR choanal atresia was first described in 1755 by Roederer in Germany.[9] Since then over 300 cases have been reported, but the entity is still uncommon.[4]

CASE REPORT

A male infant, born following an uneventful pregnancy and delivery, had feeding difficulty since birth. A cleft palate was diagnosed, and the use of a Breck feeder was moderately effective. Nipple feedings at home, however, were tolerated poorly.

He was first hospitalized at the age of 9 weeks, at which time he was malnourished and anemic. He improved with tube feeding and blood transfusions, and was discharged after 6 weeks.

Two weeks later he was again hospitalized because of swollen hands and feet, pallor, and cyanosis. Anemia was present again, with a hemoglobin level of 8.5 Gm. per 100 ml. When tube feeding was attempted 8 hours after admission, the infant began to cry, and became cyanotic and then apneic; he did not breathe for approximately 2 minutes, but finally responded to resuscitative measures. The following day 4 similar episodes of cyanosis and apnea occurred, and during the following 2 weeks of this hospitalization there were 8 additional ones.

On transfer to this hospital at the age of 4 months, the child was lethargic, did not smile, did not play, and would not follow objects with his eyes. Difficulty with feeding again arose. After taking 30 c.c. of milk the child began to cry, held his breath, and became cyanotic; then he became pale, apneic, and flaccid. After 2 minutes gasps occurred, and in 4 minutes normal breathing returned. Several attempts to pass a gavage tube through the nose failed. An attempt to pass the tube through the cleft in the palate resulted in another episode of apnea. The feeding tube was placed through the mouth, a pharyngeal airway was emplaced, and the infant was disturbed as few times as possible to prevent cyanosis. Multiple episodes of apnea and cyanosis occurred subsequently, however, one lasting 15 minutes. Death occurred during the final episode.

At autopsy, examination of the oral and nasal regions revealed a high arched palate with 2 defects in the anterior portion: a 1-cm. longitudinal defect on the right side, and a 0.2-cm. round defect on the left side. These defects connected with the anterior portion of the nose. On injection of fluid into the nose, the fluid and tenacious mucopurulent material flowed into the mouth through

*Address, Brooke Army Hospital, Brooke Army Medical Center, Fort Sam Houston, Texas.

these defects, pushing clogging exudate out of the openings. Further examination of the interior of the nose revealed a bilateral bony obstruction 2 centimeters from the anterior nares which completely sealed the posterior nasal cavities from the pharynx (Fig. 1).

No evident morphologic brain damage was discerned. There was mild fatty metamorphosis in the liver, and the subcutaneous fat was atrophic; both findings were attributed to malnutrition.

DISCUSSION

Embryologically, 3 different situations can conceivably cause posterior choanal atresia, although clinically such categorization is rarely possible.[3] They are: (1) persistence of the nasobuccal membrane of Hochstetter, which separates the nasal fossa from the primitive mouth, resulting in a typically osseous obstruction just anterior to the choanae, (2) persistence of the nasopharyngeal membrane, which separates the nasal chamber from the cephalic end of the foregut (although the immediately lower portion will have opened into the mouth to form the oropharynx), resulting in a typically membranous obstruction in the area where the hard palate becomes the soft palate, and (3) developmental variant, with the bony structures surrounding the choanal canal becoming involved in overgrowth or malposition.

Clinically, the diagnosis of choanal atresia can be made when a probe or small catheter cannot be passed through the nose; roentgen studies with a radiopaque fluid are confirmatory. Not all cases are bilateral; more than half of the reported instances are unilateral, which is a much less critical situation.[5] In the differential diagnosis of posterior nasal obstruction, other entities should be kept in mind, including hypertrophied adenoids, polyps or tumors, and cicatricial stenosis of varied causes (tonsillectomy, syphilis, diphtheria, rhinoscleroma, tuberculosis, caustic burns, trauma, or foreign bodies).[2]

The age at which the defect is discovered varies from 1 day to advanced years.[7] It is in the neonatal period that the diagnosis is most important, however, since it is one of the causes of asphyxia neonatorum which must be considered.[1]

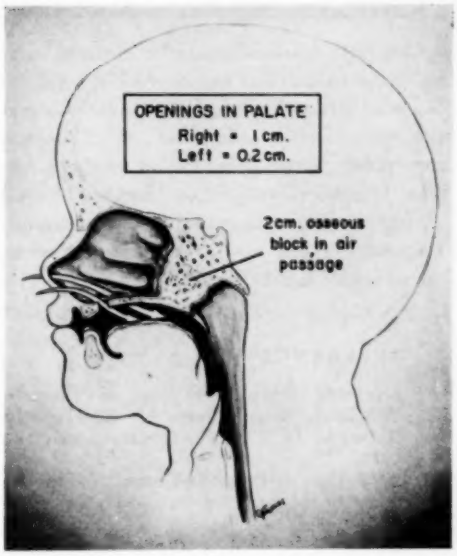

Fig. 1. Posterior choanal atresia associated with cleft palate.

Definitive treatment of this entity is tedious and long, consisting usually of rechanneling either the obstructed region or the palate.[6, 8, 10] Emergency treatment is most important, and consists of tracheotomy or some other method to ensure a patent airway.

In the case presented here the child's problems can all be attributed to the congenital anomaly in the posterior nasal cavities. This obstruction ordinarily prevents nasal breathing, but in this infant the respiratory blockade was alleviated by the congenital clefts in the palate through which air could pass through the nares and enter the pharynx and lower respiratory tract. Trouble developed only during feeding, when the bottle nipple or tongue would occlude the openings in the palate, producing complete respiratory obstruction leading to hypoxia. The development of apneic episodes, which became quite long, caused brain damage and accounted for the final deterioration. In the terminal phase, the openings in the palate became clogged by thick exudate and this accessory respiratory route was eliminated.

SUMMARY

Complete bilateral posterior choanal atresia in an infant was not diagnosed until his death at 4 months of age. Respiratory blockage was partially alleviated by a bilateral cleft palate which provided an alternate airway. This secondary pathway became blocked during feeding and resulted in increasingly frequent cyanotic apneic episodes and subsequent anoxic brain damage.

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Attempted suicides in children

Harold Jacobziner, M.D.*

NEW YORK, N. Y.

SOON AFTER the establishment of the New York City Poison Control Center in 1955[1, 2] our attention was drawn to the large number of attempted suicides in young individuals. It was our impression that the number was much greater than the ratio quoted in the literature of 5 attempts for each successful suicide.[3] This study was therefore designed to investigate the incidence of attempted suicides and other phases of the suicide problem in children and adolescents. Only those cases in which the attempt at suicide was confirmed by the family or by the individual himself were included in the study.

MAGNITUDE AND SCOPE OF THE PROBLEM IN THE UNITED STATES

Suicide is a minor cause of death under 15 years of age but, thereafter, it assumes an increasingly important role. The suicide rate for New York state in 1958 was the highest in 6 years. There were 1,091 deaths, a rate of 8.8 per 100,000. In New York City alone, 793 individuals took their own lives during the same period; the rate, 9.86 per 100,000, was the highest since 1951. The smallest number of suicides in New York City since 1900 (545) occurred in 1957 when the rate reached an all-time low of 6.7 per 100,000. The greatest number was reported during the depression years of 1931 to 1935 when there was an annual average of 1,369 suicides. The suicide rate rises in males with increasing age. In females a notable decline is observed at 60 years of age and over (Table I).

In the 10- to 14-year age group, suicide ranked thirteenth as a cause of death. In this country in 1957, 68 children between 10 and 14 years of age committed suicide; the number is greater than the number of children who died from all forms of tuberculosis and poliomyelitis combined.[4] At ages 15 to 19 suicide ranked sixth as a cause of death in the United States.[5]

In New York City suicide ranked fifth in 1958 as a cause of death between ages 15 to 19. In New York City during the 1955 to 1958 period, 39 persons under 20 years of age took their own lives. Twenty-three were males and 16 were females. Thirty-five were white and 4 were non-white. The non-white population under 20 years of age in New York is about 15 per cent of the total population under 20 years of age (see Table III). The higher male incidence and the low incidence in the non-white is observed at all ages. The most common method employed for committing suicide was by hanging and strangulation (40 per cent). The next most common means were by poisoning and jumping from high places. Only 7 per cent

This paper was presented at the Ninth International Congress of Paediatrics, Montreal, Canada, July 20, 1959.

**Address, Assistant Commissioner, Maternal and Child Health, The City of New York Department of Health, 125 Worth St., New York 13, N. Y.*

Table 1. Deaths and death rates from suicide by age and sex in New York City, 1957

Age group	*Male*	*Female*	*Suicides*		*Rate per 100,000 population*	
			Male	*Female*	*Male*	*Female*
Under 20	1,146,612	1,129,761	6	1	0.5	0.1
20 to 29	491,711	558,077	37	15	7.5	2.7
30 to 39	553,290	627,351	40	25	7.2	4.0
40 to 49	549,294	618,875	49	37	8.9	6.0
50 to 59	495,140	511,309	102	56	20.6	11.0
60 to 69	347,715	376,623	82	33	23.6	8.8
70 and over	174,380	215,333	49	13	28.1	6.0
Total	3,758,142	4,037,329	365	180	9.7	4.5

employed firearms and explosives and only one committed suicide by drowning.

Actually, the problem is even more serious than the figures indicate, since suicide as a cause of death is underreported for the following reasons.

It is often difficult to distinguish between an accidental death and a suicide. Under the current regulations used in gathering world-wide vital statistics, deaths from "undetermined" circumstances are ascribed to the accident group. Many suicides are denied by the family and are classified as accidents. A significant proportion of motor vehicle accidents, possibly 10 per cent, have a suicidal component, and probably 15 per cent of all home accidents are associated with a suicidal intent.[6] Thus, unless there is a note from the deceased or other indisputable evidence, the death is not classified as due to suicide.

Because of the marked advances in medicine and public health, deaths from other causes have declined precipitously in the past 35 years, but deaths from suicide have not had a parallel decline. Thus suicide is becoming a public health problem of increasing significance.

METHOD OF STUDY

This study was limited to children from 8 to 19 years of age who made unsuccessful attempts at suicide by the ingestion of a noxious drug or chemical.

All poisonings, whether accidental or intentional, are reported in New York City by physicians and hospitals on a prescribed form promptly after their occurrence. Following completion of treatment, a second report is submitted with additional data about signs, symptoms, treatment, and outcome.

A public health nurse visits the family in order to gain further information about motive, possible contributing factors, the method used, the home, school, and social environment, and about whether the patient was referred for psychiatric treatment. She also imparts health guidance to the family about the prevention of future suicidal attempts. These data are recorded on a specially designed form, and a register is kept on each patient. In addition, a number of patients were interviewed by a psychiatrist from the Department of Health. Most of the families were cooperative and gave information to the interviewer freely. Only 16 per cent were recorded to be evasive.

RESULTS

Two hundred and ninety-nine attempted suicides by poisoning in individuals under 20 years were reported to the Poison Control Center from March 9, 1955, to the end of 1958.

Sex and color. Distribution by sex and race is shown in Table II. There is a marked preponderance of females. The high frequency among the Puerto Ricans was not anticipated. Whereas this group makes up only 11.8 per cent of New York City's population, it is responsible for 28 per cent of the attempted suicides. Negro children also ac-

counted for a higher percentage of attempted suicides than might be anticipated from their proportionate distribution in the total population, but this difference was not statistically significant. The rate among Puerto Ricans has high statistical significance, however (Table III).

The attempted suicides among white children were proportionately lower than in the other groups. It is possible, however, that especially in white children from families of the higher economic levels, attempts are not reported at all or are reported as accidents.

Age. The highest number of attempts occurred at age 18 (Table IV). The reason for the low incidence at age 19 is not understood.

Season. The seasonal variation is shown in Table V, and corresponds with other data on the seasonal incidence of suicides. The highest incidence took place in the period of April through June (33 per cent of all attempts). The lowest number was reported during the period of October through December (15 per cent of all attempts).

CHARACTERISTICS OF INDIVIDUALS AND FAMILIES

The group did not vary appreciably from the average population in physical, mental, and emotional status. Six per cent of them had made previous suicidal attempts. Fifteen per cent gave a history of previous accidents; this is a somewhat higher frequency than was obtained in a study of accidental chemical poisonings in which only 10 per cent were found to be repeaters.

Over 50 per cent of the families were in the medium-income group and over 42 per cent were in the low-income group. The father was deceased in 8 per cent of the families involved, a rate much higher than the incidence of 1 per cent for the general accidental poisoning group in the same age category.

Supervision at time of occurrence. The mother was in the home in nearly 29 per cent of the instances at the time of the attempted suicide. No adult member of the family was present in over 50 per cent of the cases.

Table II. Attempted suicides by means of chemical agents in children 8 to 19 years of age between 1955 and 1958

	Number of cases	*Per cent of total*
Sex		
Male	67	22
Female	232	78
Total	299	100
Ethnic		
White*	143	48
Puerto Rican	83	28
Non-white*	57	19
Unknown	16	5
Total	299	100

*Exclusive of Puerto Rican.

Table III. Population under 20 years of age by ethnic group in New York City in 1957

Ethnic group	*Number*	*Per cent*
White	1,676,624	73.7
Non-white	329,749	14.5
Puerto Rican	270,000	11.8
Total	2,276,373	100.0

Table IV. Frequency of attempted suicides in children and adolescents by age

Age (years)	*Number of cases*	*Per cent of total*
9 to 12	14	5
13	28	9
14	25	8
15	42	14
16	65	22
17	53	18
18	70	23
19	2	1
Total	299	100

Reasons for attempted suicide (Table VI). Disciplinary measures, emotional upsets, and depression were listed as the chief causes.

Chemical agents. The three leading drugs employed in attempted suicides were aspirin, barbiturates, and tranquilizers. Availability and accessibility in the home were probably the principal reasons for their selection

Table V. Attempted suicides in children by month of occurrence

	Number of cases	*Per cent of total*
January to March	82	27
April to June	97	33
July to September	75	25
October to December	45	15
Total	299	100

Table VI. Reasons for attempted suicide

	1956	*1957*	*1958*	*Total*
Discipline	11	32	37	80
Emotional upset	12	13	35	60
Depression	9	18	31	58
Jealousy	9	21	11	41
School problems	—	—	14	14
Family problems	2	5	5	12
Bore illegitimate child	—	5	4	9
Drug addiction	—	1	5	6
Unknown	3	10	6	19
Total	46	105	148	299

(Table VII). In 71 per cent of the cases, the drug was in its original container. It was most frequently obtained from the medicine cabinet, and next most frequently from the bedroom and the kitchen, respectively.

Nausea and vomiting, stupor, and abdominal pain were the symptoms most frequently encountered. In 15 per cent of instances, there were apparently no symptoms. The clinical status was classified as moderately severe in about 79 per cent of the attempts and as severe in 19 per cent of the cases.

Medical care and referral. While all of the patients included in this study received adequate medical care during the acute phase, only a few children were referred for psychiatric follow-up at the time of or prior to discharge from the hospital. The public health nurse, however, who visited the home and interviewed the families later on, did make such referrals in every instance.

The role of the public health nurse. The public health nurse is the logical person to make home visits in cases of attempted suicide. In New York City public health nurses make over 250,000 home visits annually for a variety of reasons. They have an intimate knowledge of existing community resources, of the cultural and social characteristics, and of the customs and traditions of the residents in the diverse geographic areas. They are also capable of establishing easy rapport with families. Families tend to accept home visits from public health nurses more readily than from any other member of the health professions. The nurses who made the home visits received prior orientation from the consultant nurses in child health and in mental health.

The families did not seem to consider the nurse's visit as a threat, were cooperative in most instances, and imparted information freely.

The nurse did not limit her interview to the specific episode; she also explained the emotional and social development of adolescents to the family. In addition, the nurse helped families with other health problems. She gave information concerning health supervision and immunization for infants and preschool children and concerning prenatal care for expectant mothers. She also looked for accident hazards and gave suggestions on safety measures. Whenever indicated, follow-up visits were made to provide further guidance.

DISCUSSION

A striking feature of this study was the high ratio of suicidal attempts to successful suicides (50:1). There were only 8 suicides in over 400 reported attempts in this series of attempted suicides by means of a drug or a chemical. If this ratio prevailed among adults, there would have been over 39,000 attempts at suicide in New York City alone during 1958, or one attempt per 200 individuals of the city's population. The reports of attempts at suicide by adults are not as comprehensive as they are for individuals under 21 years of age; only 3,177 poisonings, fatal and nonfatal, including suicides and suicidal attempts, were recorded in persons over 19 years of age during 1958.

Table VII. Attempted suicides by means of chemical agents

Chemical agent	*Number of cases*	*Per cent of total*
Aspirin	84	28
Barbiturate	47	16
Tranquilizer	36	12
Bleach	26	9
Mixture of drugs	26	9
Iodine	19	6
Insecticide	13	4
Lye	9	3
Alcohol	9	3
Miscellaneous	28	9
Unknown	2	1
Total	299	100

The incidence of suicides varies with age, sex, color, culture, season of the year, and socioeconomic status.[7-10] Whereas suicides are more common among the male population and the frequency increases with advancing age, among females attempts at suicide are more common in the young. In our series, over three-fourths of the attempts at suicide were made by females, and the incidence among adolescents (under 20 year of age) was higher than in later years.

The reason for the high incidence of attempted suicides in females and in adolescents is probably due to the greater impulsiveness of the young female, who does not premeditate the act, nor actually desire to die. It is, in the main, a precipitous impulsive act, a sudden reaction to a stressful situation. It is possible that many accidents, particularly in children with a history of "repeatism" or accident proneness, are perhaps subconscious attempts at suicide.

Shneidman and Faberow[11] found that 75 per cent of adults who committed suicide had made previous attempts or threats. Fifty per cent committed suicide within 3 months after having passed an emotional crisis from which they actually appeared to be recovering. The individuals who threatened suicide were apparently more disturbed emotionally than were the ones who attempted it. The attempt apparently has a therapeutic effect in some instances. The authors wisely caution us to consider seriously both threats and attempts, to observe the person carefully, and to provide psychiatric help for at least 3 months following the attempt. Schmidt and associates[12] in their evaluation of attempted suicides found that 26 per cent have made at least one unsuccessful previous attempt. Repeated attempts were most frequent in the "psychopathic personality group." Two persons in Schmidt's group of 109 eventually killed themselves.

Thirty-five per cent in this group told someone of their plan prior to the attempt, but only 8 per cent told their physician, though 57 per cent were under a physician's care. Physicians generally do not think of suicide when taking a history. A statement about suicidal preoccupations or attempts is an important indication, and Schmidt advises hospitalization of all patients who make serious attempts.

The problems of adolescents differ from those of the young child.[13, 14, 15] The adolescent has 3 major preoccupations: (1) a drive for independence, i.e., emancipation from family restriction, (2) sex adjustment, and (3) recognition from peers. The adolescent has two sets of rules to live by, those laid down by adults and the ones prescribed by his peers. Though striving for independence, he is worried about assuming independence and its associated responsibilities and often craves for the dependence which he had during childhood.

Thus he often appears inconsistent and contradictory in his behavior. He becomes ambivalent, secretive, and impulsive. He is constantly trying to find himself and to become identified as an individual. Adolescence is a period of rapid growth and development, physical, mental, and psychosocial. It is a critical period associated with many emotional and social conflicts, tensions, pressures, stresses, and home and school difficulties and adjustments. He has a feeling of self-consciousness and great concern about his spurt of growth. Because of his psychosocial and sexual conflicts, his interpersonal relations are often stormy. Parents, teachers, physicians, and all concerned with adolescents could help them to grow up into mature

adults by treating them with respect, sympathy, and understanding. When adolescents are subjected to many frustrations they feel unwanted, insecure, and alone, and often resort to suicidal attempts.[16] These attempts do not necessarily result from mental illness.

PREVENTION OF SUICIDES AND ATTEMPTED SUICIDES

Suicides and suicidal attempts in adolescents are of multiple causes. They are chiefly due to unresolved conflicts, frustrations, disappointments, guilt feelings, loss of self-esteem, fear of punishment, and the real or imaginary loss of a love object. The motivating force is aggression, usually directed toward the love object, and serves as a means of punishing parents. It is an act of hostility against a restraining figure.[17, 18, 19] According to Schechter,[20] children develop feelings of rage toward the frustrating object, as well as feelings of helplessness, and they become depressed and utilize a number of defense mechanisms. When the defense mechanism breaks down, an attempt at suicide may be made.

Many of the children in our series who attempted suicide came from broken, unstable, and disorganized homes resulting from death, separation, or divorce of parents. In the main, stable homes produce stable adolescents. Adolescence requires great adaptability and the degree of adaptability to stress and strain depends largely on earlier experiences, health status, and the parent-child relationships.

Therapy of attempted suicide is in actuality prevention. The would-be "suicide" and all who attempt suicide constitute a vulnerable group and should be identified and "immunized" against suicide. Warning signs which help in the early detection of the child susceptible to suicide are a sudden change in personality or behavior, agitation, anxiety, irritability, depression, anorexia, insomnia, and frequent and otherwise unnecessary outbursts of temper. Listening to adolescents in times of need and showing an understanding and sympathetic attitude may be lifesaving.

Education is the keystone to prevention. Physicians must acquire a greater awareness of and interest in the problems of suicide prevention. Teachers and parents must have a better understanding of the particular problems, needs, interests, and reactions of adolescents, and they must exhibit greater sympathy and understanding in dealing with them.

Adolescents who have attempted suicide should be referred to a physician. He should review the situation with the adolescent and the parent. The discussion should be directed toward the patient's conflicts, his emotional and social problems, his preoccupation with school, peers, sex, and any other difficulties which may become apparent. The adolescent's interrelationships within the family and his interpersonal relationships outside the family should be brought out. If the physician finds a deep-seated underlying emotional disturbance, psychiatric care is needed. The psychiatric care is far more important, in many instances, than the emergency medical care provided. This responsibility should also be shared by the hospital administrator.

Every attempt at suicide should be reported to a central agency to ensure that all children who may be considered to have suicidal potentialities will receive supervision and guidance. Periodic home visits by a visiting nurse to determine whether the patient is under treatment and to help the family with existing social problems is indicated. The family and the community, including the church, must be prepared for the patient's return home if he has been hospitalized; his acceptance into the family and the community without stigma should be assured. Such acceptance is essential to avoid recurrences. Mental health consultation and guidance should also be provided for other members of the family, since these experiences are traumatic for the entire family.

SUMMARY AND CONCLUSIONS

1. Data are presented on 299 confirmed unsuccessful attempts at suicide by means of ingestion of a drug or chemical by adolescents in New York City.

2. A striking ethnic difference was observed; the incidence among Puerto Ricans is much higher than among any other group.

3. A high incidence was also observed in children who came from broken and disorganized homes.

4. A seasonal pattern was noted; the incidence was lowest in the autumn and highest in the spring.

5. Attempted suicide is relatively frequent during adolescence; there was a ratio of at least 50 attempts for every actual suicide.

6. Unlike suicide, which is more frequent in the high income group, the majority of attempted suicides occurred in the medium- and low-income groups.

7. Means for prevention of suicide are suggested.

8. Follow-up and aftercare including guidance to the family of the child who has attempted suicide are recommended.

9. The pediatrician and the general practitioner must play a greater role in the prevention of suicide.

Grateful acknowledgments are expressed to Dr. Harry Bakwin for his valuable suggestions. Thanks are expressed to Miss Elizabeth Mahoney, child health nurse consultant, and to the many public health nurses for making the home visits.

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TROPICAL PEDIATRICS

Malignant tumors in African children

With special reference to malignant lymphoma

G. T. O'Conor, M.D.,* and J. N. P. Davies, M.D.

KAMPALA, UGANDA, EAST AFRICA

LITTLE attention has been directed specifically to the subject of neoplasia in African children, and no paper appears to have been published to date dealing with this special problem. This is not surprising, for in large areas of undeveloped, underdeveloped, and recently developed Africa diagnostic facilities are limited almost to the individual's clinical acument and skill in the interpretation of physical signs. Laboratory services are at a minimum and immediate pathologic consultation, save in some of the largest centers, is usually nonexistent. Particularly in the field of cancer has this led to many misleading and contradictory statements in both the medical and the popular literature.

Cancer was once thought to be rare in Africa, but now the pendulum has swung and cancer is believed to be as common as, and perhaps even more common than, in other countries. Most regard this not as a true increase in incidence but only an apparent one due to a host of factors concomitant with economic and educational development, although Schweitzer[1] believes it to be, in fact, genuine, and attributes it, perhaps, to certain dietary factors and habits introduced with European immigration. The morbidity of cancer in all countries is uncommon relative to infectious and degenerative disease, and any one physician's experience with cancer is necessarily limited unless he is working as a specialist or in a cancer hospital. This is even more a reality in Africa where infectious and parasitic disease is so abundant. Moreover, the cases of cancer that clinicians do see are often in a late stage, beyond hope of surgical relief, and no other form of treatment is generally available. Resort to diagnostic refinements such as surgical biopsy is not made and clinical diagnoses are often the only ones available. Hence, accurate information on neoplasia in Africa is very scant, and prior to the present decade was based on impression, hearsay, and, at best, limited biopsy and autopsy material.

From the Department of Pathology, Makerere College Medical School and Mulago Hospital, Kampala, Uganda, East Africa, and from the Kampala Cancer Registry.

The Kampala Cancer Registry is financed by Grants from the British Empire Cancer Campaign.

**Address: Makerere College Medical School, P.O. Box 2072, Kampala, Uganda, East Africa.*

Of the published reports more recently available, there is only little reference to the disease as it affects children. Gelfand,[2] reporting 2,000 autopsies in Rhodesia from 1946 to 1948, saw 74 malignant growths, but only 3 of these were in children. Davies and Wilson[3] reported a small series from Uganda, and Thys,[4] from Stanleyville in the Belgian Congo, has reported that of 2,529 malignant growths over a 16½ year period 96 were in the age group 0 to 9 years. Although in the latter paper the material is not entirely comparable to ours, the incidence by histologic type would seem to be very similar to our experience as reported here. Bras[5] has recently reviewed the knowledge of malignant neoplasm in children in the tropics; he admits that little accurate data are available and reviews the many problems inherent in the collection of such data for comparison with incidence figures in European countries.

THE KAMPALA CANCER REGISTRY

This communication has as its purpose to record the experience of the Kampala Cancer Registry during its 7 years of existence in respect to malignant tumors of children and to elaborate on some of the significant observations. The Registry was instituted in 1951, and the details of its organization and operation have been previously described.[6] Although it is considered likely that the Registry obtains information on all patients with cancer who seek medical care in Kampala, it necessarily has a relatively small scope and is concerned with a limited area which has reasonably well-developed medical facilities. There are profound difficulties and a myriad of factors limiting interpretation of the data obtained, the chief one being the uncontrolled selection of cases. This is affected by the patient's natural selection as to whether or not he will present himself or his children to the hospital, whether he will allow biopsy or extirpative procedures, and, finally, whether relatives will permit postmortem examination. The medical staff makes a further artificial selection as to teaching material, the possibility of being able to offer more than palliation, and often by the current spheres of interest of the professional staff.

The Kampala Registry records only the case seen in the Kampala hospitals and, although biopsy specimens sent from outlying and up-country hospitals and dispensaries are not included, many of the malignant cases are ultimately referred to Kampala. It is, therefore, impossible to say with any exactness what total population the Registry embraces and thus compare incidence rates with other series. Accurate census figures with age-grouping are being prepared for a limited district in the Kampala area so that such rates may be truly compared with rates in other countries and geographical areas.

Table I. Malignant tumors in African children (microscopically confirmed, 1952-1958)

Epithelial carcinoma		6
Adenocarcinoma, liver	1	
Transitional cell carcinoma, kidney	1	
Adenocarcinoma, thyroid	2	
Adenocarcinoma, salivary gland	1	
Adenocarcinoma, primary site undetermined	1	
Melanoma		3
Eye	2	
Skin	1	
Leukemia		7
Myeloid	5	
Lymphatic	2	
Lymphoma		60
Lymphosarcoma	57	
Hodgkin's	3	
Connective tissue sarcoma		18
Fibrosarcoma	8	
Rhabdomyosarcoma	3	
Kaposi	3	
Nonlipid reticulohistiocytosis	2	
Botryoides	1	
Osteogenic	1	
Tumors of neural origin		14
Retinoblastoma	9	
Neuroblastoma	3	
Argentaffinoma	1	
Neurofibrosarcoma	1	
Tumors of embryonal and mixed tissues		17
Nephroblastoma (Wilms')	13	
Salivary gland	2	
Teratoma	2	
Total		125

Table II. Clinical diagnosis only (1952-1958)

Intracranial tumor	5
Orbital tumor	5
Sarcoma of jaw	10
Cervical lymphadenopathy (massive)	5
Abdominal mass (inoperable)	22
Wilms' tumor	2
Osteogenic sarcoma (x-ray)	4
Soft tissue sarcoma	3
Miscellaneous	4
Total	60

CASE MATERIAL

In this study all malignant tumors occurring in African children from 0 to 14 years of age which are recorded in the Kampala Registry from 1952 to 1958, inclusive, have been reviewed and classified. Table I lists 125 cases and describes all which were confirmed by biopsy and/or autopsy. They are listed by histologic type with use of a modified and condensed classification based on the *Manual of Tumor Nomenclature and Coding* of the American Cancer Society.[7] In Table II are listed 60 additional cases in which histologic confirmation could not be obtained but where clinical and roentgenographic evidence was virtually conclusive as to the malignant nature of the given lesion. This makes a total of 185 new malignant cases in children in a 7 year period, an average annual incidence of 26.

In Table III a further condensation to the principle histologic groups is made, and actual numbers of recorded cases are compared with three other large published series in the United States. The Andersen series[8] represents all malignant tumors of children seen at the Babies Hospital, New York, over a 16 year period. The Connecticut Study[9] is the result of a 17 year period of registration of all tumors in a small state of 2 million people, while the United States Public Health Service report by Dorn and Cutler[10] is a one year study of tumor incidence in 10 metropolitan cities representing a total population of 14.6 million.

Although, as noted above, it is not possible to compare total incidence figures because of the indefinite area and population from which our cases are drawn, it does seem reasonable to assume that the Kampala series is at least a significant and representative sample of malignant disease as it occurs in East African children. This, we believe, applies also to the pattern of histologic types and, thus, this pattern as indicated by the percentage of total tumors is a true one. It is, then, permissible and useful to make comparisons with the other series on the same basis and this is done in Table IV.

Discussion. Study of the tables reveals many similarities in the American and Kampala series, although there are also some striking differences. Three of these appear to have statistical significance and bear discussion.

First, there is the low frequency in our series of a tumor generally recognized as one of the most frequent types occurring in children—neuroblastoma. Previous experience in Kampala had suggested that neuroblastoma was, in fact, a relatively common tumor of African children,[3] but this is now realized to be in error. The difficulty arose in part from confusion with the malignant lymphomas and their peculiar distribution. The comparative infrequency, now realized, of these primitive neural tumors is not easily explained. One important factor may be that they are tumors of the very young ages, in which the mortality rate from malaria and other infectious diseases is at its highest. It may also be partly due to some factor of selection so far not evident, and longer experience may well alter these figures.

The second striking point of variation in the comparative data is the rarity of leukemia in the Kampala series, as compared both with the other series listed and with many other published reports.[11] This rarity of leukemia in African children has been previously observed and reported.[12, 13] It is likely that some cases have been missed as a result of patient load and lack of trained laboratory technicians. Against these factors tending to diminish the likelihood of diagnosis should be set two factors tending to increase the chances of diagnosis. One is the frequency of malaria which predicates the

Table III. Comparative incidence of microscopically confirmed cases of cancer in children

	K.C.R. (1952-1958)	*Andersen (1935-1950)*	*Connecticut (1935-1951)*	*U.S.P.H.S. (1947)*
Epithelial carcinoma	6	12	22	31
Melanoma	3	0	20	12
Leukemia	7	40	191	136
Lymphoma	60	19	78	49
Connective tissue sarcoma	18	35	79	75
Tumors of neural tissue*	14	49	131	86
Tumors of embryonal and mixed tissues	17	20	65	32
Others	—	—	8	4
Total	125	175	594	425

*Neuroblastoma is included in this group.

Table IV. Comparative incidence of microscopically confirmed cases of cancer in children (per cent of total)

	K.C.R. (1952-1958)	*Andersen (1935-1950)*	*Connecticut (1935-1951)*	*U.S.P.H.S. (1947)*
Epithelial carcinoma	4.8	6.9	3.6	7.3
Melanoma	2.4		3.4	2.8
Leukemia	5.6	22.8	32.2	32.0
Lymphoma	48.0	10.9	13.2	11.5
Connective tissue sarcoma	14.4	20.0	13.3	17.8
Tumors of neural origin*	11.2	28.0	22.0	20.2
Tumors of embryonal and mixed tissues	13.6	11.4	11.0	7.5
Others	—	—	1.3	.9
Total	100.0	100.0	100.0	100.0

*Neuroblastoma is included in this group.

examination of a blood film for each sick child whatever the clinical diagnosis or state of the child. The second is the frequency in African children of anemia, splenomegaly, and general lymphadenopathy, which, to the European trained clinician of Kampala, almost invariably suggests the necessity of excluding a diagnosis of leukemia. Thus, it is believed that the incidence of leukemia is truly lower in Kampala than elsewhere and that the infrequency is a genuine difference and not one of selection, interpretation, or insufficient evidence. It is perhaps noteworthy, in addition, that of the 7 registered cases of leukemia 5 were of the myeloid type.

Paradoxically and perhaps of related significance, the third major difference in these compared series is the very high number of malignant lymphoma reported from Kampala. These are by far the most common tumors seen here in African children and constitute almost one half of the recorded malignancies. They will be discussed in more detail below.

Since malignant lymphoma in this study has replaced lymphatic leukemia as the most common neoplasm of childhood, it is suggested that this may represent a true variation in the site of malignant proliferation and, more important, an alteration in the natural history and course of the diseases of the lymphopoietic system. Further experience and expansion of our investigation of this subject should serve to confirm and elucidate or refute these speculations.

MALIGNANT LYMPHOMA

Since almost half of the tumors in this series of malignant growths in African children have been classified as lymphoma, spe-

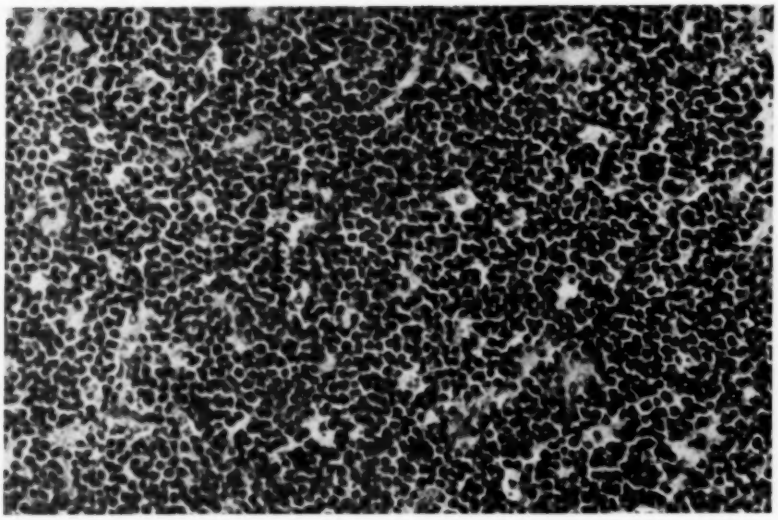

Fig. 1*A*. Typical histology illustrating cellularity and "water pot" effect. (×400; reduced ¼.)

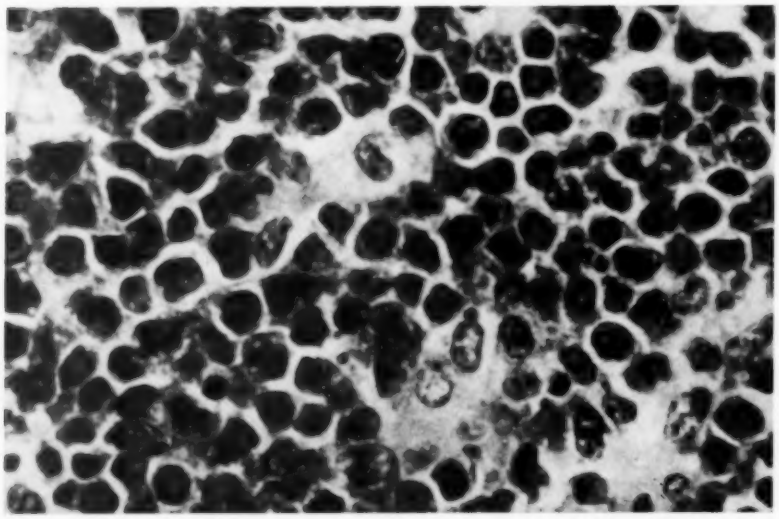

Fig. 1*B*. Immature lymphoid cells predominate but scattered "reticulum" cells are also present. (×800; reduced ¼.)

cial attention here is warranted. Gall and Rappaport[14] have succeeded, at last, in presenting a workable classification of this group of neoplasms which should be acceptable to pathologists and clinicians alike and which we have readily adopted. Of the 60 cases in our series which represent 48 per cent of the total malignancies recorded, three were both clinically and histologically typical of Hodgkin's disease. In all of the rest, the histology

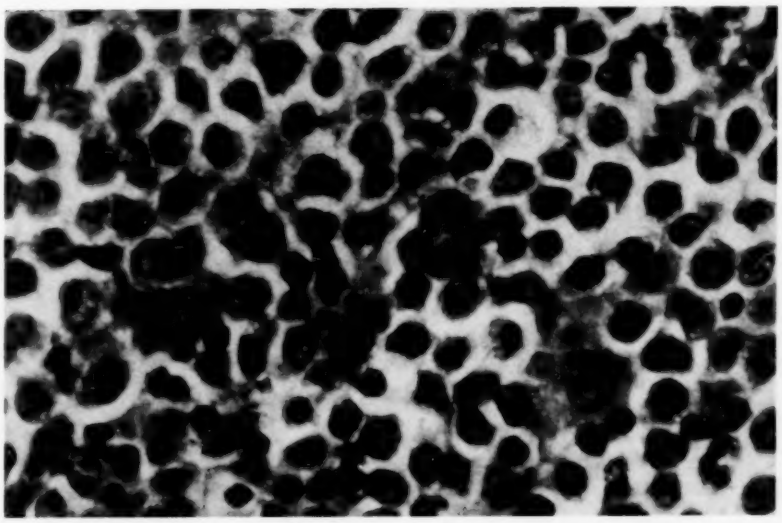

Fig. 1*C*. Immature lymphoid cells predominate but scattered "reticulum" cells are seen. (×800; reduced ¼.)

was remarkably uniform and they have been subclassified as poorly differentiated lymphocytic lymphoma or "lymphosarcoma" (Figs. 1*A*, 1*B*, and 1*C*). The predominant cell type is similar to a lymphoblast with a large immature nucleus and only a thin rim of cytoplasm. Sheets and masses of cells are supported on a delicate reticulin stroma. The so-called "water pot" effect with tumor cells surrounding one or more swollen stem cells or histocytes is very prominent and in our laboratory has become almost a trade-mark by its frequency in these lesions. Mitoses are abundant, and rapidity of growth, an important clinical characteristic, is indicated by large areas of necrosis and, in some sites, particularly the jaw, by secondary infection. Details of histopathology and cytogenesis are to be discussed in detail elsewhere.

PRESENTING SITE AND ORGAN DISTRIBUTION

Apart from their high incidence, the most striking feature of these tumors is their distribution, with regard to site and organ. In 29 cases the malignant growth presented as massive and destructive lesions in either the mandible or maxilla or in both (Figs. 2*A*, 2*B*, and 2*C*). Burkitt[15] has described some of the clinical features of these tumors. The history is characteristically very short. This may be due to the fact that the onset is dated by the parent from the time secondary infection, necrosis, and hemorrhage resulted in a sudden increase in size or in fever and pain. On the other hand, the tumors have been seen to grow with extraordinary rapidity, and changes in the outline of the face can be seen every 24 hours in carefully observed cases. They progress rapidly to death, or the children may be removed from hospital in a moribund condition. The tumors may present in one or more quadrants of the jaw, but even when only one quadrant is clinically involved radiologic studies will usually show areas of osteolytic destruction in all four quadrants.[16] The earliest roentgenologic appearance suggests that the malignant proliferation starts in the marrow spongiosa, in relation to the lamina dura of the developing teeth, and expands outward causing the teeth to erupt and fall out.

Of the 29 patients presenting in this fashion, 16 had no gross clinical evidence of extra jaw neoplasm at the time of initial observation, 10 had proved tumor elsewhere,

Fig. 2*A*. Clinical appearance of child with mandibular lesion in late stage.

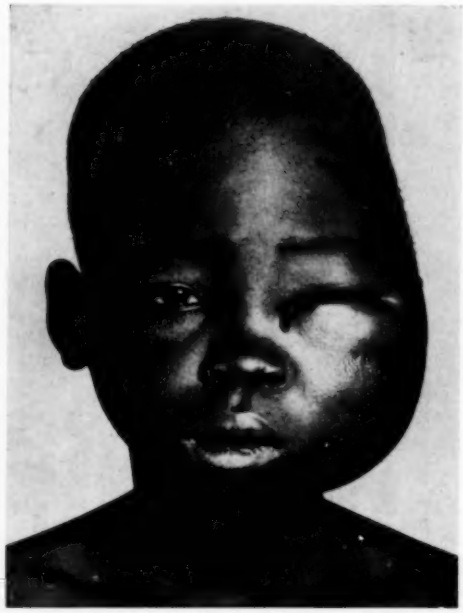

Fig. 2*B*. Clinical appearance of child with maxillary lesion extending into orbit in late stage.

and the remaining 3 had clinical evidence only of hepatic involvement. Six of the patients were autopsied, and all showed extensive abdominal organ or other visceral infiltration as well as lymph node involvement. The latter was chiefly in the retroperitoneal groups, marked peripheral adenopathy being uncommon.

The child with a large abdominal mass comprises the second most common clinical group, and in 20 cases the malignant lymphoma presented in this manner. At laparotomy or autopsy massive enlargement of either the retroperitoneal lymph nodes or of one or more parenchymatous organs due to extensive infiltration was found (Figs. 3*A* and 3*B*). The presenting sites or complaints in the other 11 cases are listed in Table V. Twelve of these non-jaw cases came to autopsy and showed multifocal tumor deposits and lymph node replacement in the same general distribution as did the "primary" jaw cases.

The organ involvement in the 18 autopsied cases is shown in Table VI. Apart from the features noted above, there are a number of other points worthy of note. In gross appearance the tumors were soft pink or white masses mottled with hemorrhage or necrosis. Multiple nodules or irregular masses of such tumor tissue were deposited in, or virtually replaced, the organs listed. In some instances, the organ infiltration was only microscopic. The lymph nodes involved were most frequently the celiac and periaortic groups. While marked peripheral adenopathy was usually notable by its absence, multicentric development of neoplasia within the germinal centers was frequently observed in lymph nodes which were not particularly enlarged. Curiously, the spleen was very often spared.

DISCUSSION

The relationship and nomenclature of these jaw and non-jaw tumors which consti-

tute such a large percentage of malignant growths in African children has been a matter of speculation and local controversy for some time. Consideration of them as a group and restudy of the sections have shown quite conclusively that they are in fact the same type of tumor, are derived from the primitive cell of the lymphoreticular system, and should thus be classified as malignant lymphomas. In both groups the histologic appearance is identical and it is not possible to differentiate jaw and non-jaw cases by examination of slides. Both progress steadily to the death of the child and, except for the initial localization, show identical lesions and distribution at autopsy. Neither is associated with specific changes in blood or urine. In no instance was there a peripheral blood picture indicative of leukemia at the time of diagnosis, and only one patient developed subsequently and terminally evidence of leukemia in the peripheral blood.

The frequency of malignant lymphoma found in this study, as well as the possible inverse relationship to leukemia, has been stressed. This may be further emphasized by a comparison of our 57 cases (excluding Hodgkin's disease) in the 0 to 14 age group with the 69 lymphosarcomas among children 15 years old or younger which constitute a 30 year experience at Memorial Hospital in New York, recently reported by Rosenberg and associates.[17] The same authors have also pointed out two characteristics peculiar to lymphosarcoma of children: the local aggressiveness which leads to rapid death before extensive spread occurs and the fact that in children extranodal sites often appear to be the primary focus. These features are most evident and are certainly characteristic of the disease as it occurs in East Africa.

The astounding incidence of localization in the jaw in our cases is indeed unique and would seem to be a real geographic or epidemiologic phenomenon. Other bones are rarely involved even secondarily, and the histology and clinical behavior is quite unlike the primary reticulum cell sarcoma of bone first described by Jackson and Parker[18] and further characterized by Coley and co-

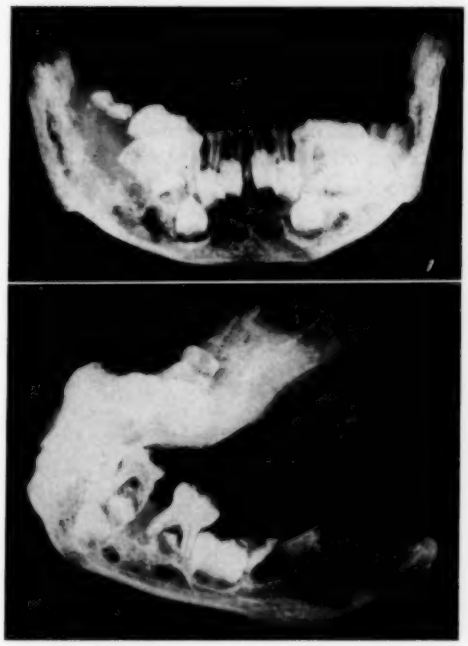

Fig. 2*C*. Roentgenographic appearance of mandible in a surgical specimen.

workers.[19] Such tumors as we have reported are seen in other parts of East and Central Africa, in the Rhodesias, the Belgian Congo, and probably in West Africa, and are variously diagnosed clinically as osteomyelitis, adamantinomas or histologically as osteogenic sarcoma or simply round cell sarcoma. Existence of the jaw localization outside Africa is apparently very rare if it exists at all, but it may occur in other parts of the tropics. A male predominance of 3:1 in the jaw tumors as opposed to an almost even sex distribution in the nonjaw tumors may

Table V. Malignant lymphoma: presenting site or complaint

Tumor of jaw	29	
Abdominal mass	20	
Cervical adenopathy	5	(3 of these Hodgkin's)
Soft tissue swelling	4	
Testicular enlargement	1	
Paraplegia	1	

have epidemiologic significance but is more likely simply a reflection in this small series of the well-recognized male preponderance of lymphoma. An unusually high incidence of jaw tumors in adult Africans[16] further indicates an unusual affinity of the African jaw for neoplasm. However, in the adult the main type of tumor is the adamantinoma which is certainly dissimilar and without obvious histogenetic connection to the malignant lymphoma. Further epidemiologic studies are in progress to more clearly define and perhaps elucidate this problem.

Table VI. Malignant lymphoma: incidence of involvement of different organs in 18 autopsied cases

Lymph nodes	15
Kidneys	12
Liver	11
Adrenal	10
Bone (jaw)	7
Bone (other)	2
Pancreas	5
Intestine	5
Thyroid	5
Stomach	4
Heart	4
Salivary gland	2
Soft tissue	2
Gall bladder	1
Testicle	1
Pituitary	1
Brain	1
Tonsil	1

Fig. 3*A*. Autopsy specimen showing bilateral and symmetrical massive enlargement of kidneys and ovaries in 5-year-old girl.

Fig. 3*B*. Cut surface of kidney in same patient as Fig. 3*A*, showing the diffuse parenchymal replacement.

No comments concerning therapy are pertinent here since radiotherapy is not available in East Africa at present and experience to date indicates that the multicentric origin, as well as the advanced state of patients when first seen, precludes surgical approach to either the jaw or non-jaw tumors. In a few cases nitrogen mustards have been used but with disappointing results.

SUMMARY

1. The incidence and histologic classification of malignant tumors in African children as recorded by the Kampala Cancer Registry from 1952 to 1958 are reported.

2. The infrequency of leukemia in African children, previously observed, is confirmed.

3. Malignant lymphomas are the most common tumors recorded and constituted almost 50 per cent of the total malignant growths in this series.

4. The incidence and distribution of malignant lymphoma as well as a marked reversal of the leukemia to lymphoma ratio

suggests a significant difference in the natural history of lymphopoietic tumors in African children.

5. The very frequent and apparent primary origin of lymphoma in the jaw indicates an unusual affinity and suggests a local causative factor.

We are grateful to Mrs. D. M. Davies, Mrs. R. M. Coles and the staff of the Cancer Registry, and Dr. A. G. M. Davies for the radiographs and to Mr. P. Cull for the clinical photographs and charts. The Histopathology Section is under the technical direction of Mr. R. Tunnicliffe, F.I.M. L.T.

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MEDICAL PROGRESS

Digitalis therapy in infants and children

Saul J. Robinson, M.D.*

SAN FRANCISCO, CALIF.

DIGITALIS, the most effective drug known for the relief of congestive failure and a potent drug for the conversion of many of the arrhythmias, has many idiosyncrasies. The myocardial effects of digitalis are apparent only in cardiac failure, and then not in all types of failure. It has little effect in the mechanical types of heart failure such as constrictive pericarditis, in extensive involvement of the myocardium as in rheumatic carditis, or in any disease process replacing myocardial fibers as in sickle cell disease or Friedreich's ataxia. It may afford little improvement in the high output failure associated with anemia, thyrotoxicosis, beriberi heart, Paget's disease, or arteriovenous fistulas, because in these the failure is precipitated by increased body needs rather than by intrinsic myocardial insufficiency. Therefore, it is in the so-called low output types of failure that digitalis has its greatest effectiveness.[1]

Congenital heart disease is probably the leading cause of heart failure in infants and children.[2] Since 80 per cent of heart failure in the pediatric age group occurs in infants, the recognition and proper treatment of this condition in that age group are extremely important.[3] Cardiac decompensation in infancy may occur with transposition of the great vessels, patent ductus arteriosus, large ventricular septal defect, coarctation of the aorta, endocardial fibroelastosis, and less commonly with severe pulmonic or aortic stenosis. It may also occur with many of the metabolic diseases as well as with viral myocarditis of infancy, paroxysmal tachycardia, erythroblastosis with severe anemia, and possibly hyaline membrane disease.

Diagnosis sometimes presents a difficult problem. Tachypnea, tachycardia, cardiomegaly, fatigability, and hepatomegaly are the classical signs that may be found in infants and children with congestive failure. Edema and increased venous distention are rarely present in this age group and are difficult to recognize. Pulmonary râles, when present, are difficult to differentiate from those due to the frequently associated pulmonary infection.

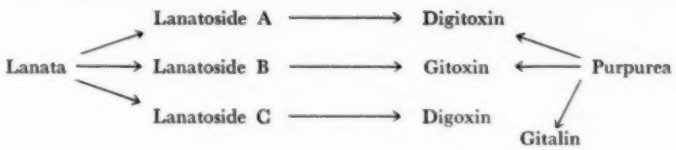
DIGITALIS PHARMACOLOGY

Preparations of digitalis are derived from two families of drugs: *Digitalis purpurea* and *Digitalis lanata*. The activity of the preparation depends essentially on the glycosides which it contains.[4]

Table I shows the breakdown products of *Digitalis purpurea* and *Digitalis lanata*. It can be noted that digitoxin and gitoxin may be obtained from either crude drug, but digoxin, or Lanoxin as it is now called, is ob-

*Address, 2215 Post Street, San Francisco 15, Calif.

Table I. Pharmacology of digitalis



tained only from *Digitalis lanata,* and gitalin (Gitaligin "White") is obtained only from *Digitalis purpurea.*

Digitalis purpurea consists of a great deal of inert matter and several natural glycosides. At the present time, it can be assayed biologically only by its lethal effects in pigeons. The same biologic standards were previously used on cats, from which the term cat unit as a method of standardizing digitalis was derived. Apparently, at one time, cats were becoming too scarce or too expensive for this use, and the biologic assay of digitalis was transferred from the cat to the pigeon.

BIOCHEMISTRY OF DIGITALIS

Suggestions regarding the biochemical site of digitalis action are being adduced from studies on the contractile elements of muscle. According to the ideas of Szent-Gyorgyi,[5] the contractile system of muscle consists of an elongated protein conjugate, myosin, and its precipitin, polymerized actin. In the presence of potassium ions and using adenosinetriphosphate (ATP) as an energy source, the muscles contract. On the basis of clinical experience, it may, therefore, be anticipated that digitalis affects in some manner the contractile elements themselves or the concentration of intracellular potassium that moderates contractile action.

PHYSIOLOGIC ACTION OF DIGITALIS

Digitalis probably works by two separate mechanisms on the heart. When small doses are administered, the heart rate is slowed down because the drug acts on the vagus nerve; this process may be abolished by atropine or exercise. As the dosage is increased, however, a direct myocardial action takes place which may cause further improvement without alteration in the heart rate. The myocardial action of digitalis increases the force of the systolic contraction of the heart muscle without alteration in the size of the diastolic fiber. This more forceful contraction results in more complete emptying of the ventricle, and thus increase in stroke volume. The duration of systole is abbreviated, giving more time for both ventricular filling and heart rest in diastole. Since the initial diastolic fiber length is associated with the amount of oxygen consumption, a reduction in its size diminishes the amount of oxygen utilized, resulting in an increase in cardiac efficiency and output. Hence renal blood flow, glomerular filtration, and urine output are increased while venous pressure and extracellular fluid are decreased.[6]

The physiologic actions of digitalis may be summarized as follows: (1) the ventricular rate falls, (2) the cardiac output increases (only in failure), (3) the arteriovenous difference decreases, (4) the peripheral venous pressure falls, (5) the right atrial pressure falls, (6) the pulmonary arterial diastolic pressure falls, (7) the conduction time between the atrium and ventricle decreases, and (8) the A-V and S-A nodes are depressed.

PREPARATIONS OF DIGITALIS

Dosages in this paper and in Tables II and III are given in milligrams per pound. While this may appear inconsistent, experience seems to indicate that almost all hospitals, except perhaps university hospitals, use pounds rather than kilograms in charting the weights of children in the nurseries and pediatric wards, though the advisability of this method can be questioned. It is far easier for anyone wishing to determine the dosage

Table II. Characteristics of digitalis preparations

Agent	*Method of administration*	*Onset of action*	*Maximal effect*	*Duration of effect*	*Maximal duration of toxicity*
Digitalis leaf	Oral	6 hours	12 to 48 hours	17 days	1 to 2 weeks
Gitalin	Oral or intravenous	1 hour	6 to 8 hours	7 to 10 days	3 to 7 days
Digoxin (Lanoxin)	Oral or intramuscular	2 hours	6 to 8 hours	4 to 7 days	2 days
	Intravenous	3 to 8 minutes	2 to 3 hours		
Lanatoside C or D	Intravenous or intramuscular	7 to 9 minutes	2 to 3 hours	2 to 3 days	1 day
Digitoxin	Oral	2 hours	2 to 9 hours	21 days	21 days
	Intravenous or intramuscular	30 minutes	2 to 9 hours		

Table III. Dosage of digitalis preparations for infants and children (infant, under 2 years of age; child, 2 to 12 years of age)*

Agent	*Method of administration*		*Total digitalizing dose (mg./pound)*	*Maintenance dose*
Digitalis leaf	Oral	Infant	15	1/10 total digitalizing dose
		Child	10	
Gitalin	Oral or intravenous	Infant	0.05	1/10 to 1/5 total digitalizing dose
		Child	0.05	
Digitoxin	Oral or intravenous or intramuscular	Infant	0.02 – 0.03	1/10 total digitalizing dose
		Child	0.01 – 0.02	
Digoxin (Lanoxin)	Oral	Infant	0.03 – 0.04	1/10 to 1/4 total digitalizing dose
		Child	0.02 – 0.03	
	Intravenous or intramuscular	Infant	0.02 – 0.03	
		Child	0.01 – 0.02	
Lanatoside C or D	Intravenous or intramuscular	Infant	0.01 – 0.02	Usually not used
		Child	0.008 – 0.01	

*Recommended method of administration with consideration of individual variation: one-half total dose at once followed by one-fourth total dose in 6 to 8 hours, and one-fourth total dose in another 6 to 8 hours, with maintenance therapy instituted 12 hours thereafter.

in kilograms to multiply by 2.2 than it is to submit a duplicate set of figures, since the wrong set could be used when dispensing the drug. Such a mistake would be very serious since the therapeutic to toxic ratio of digitalis is one of the smallest ratios of all drugs used in medicine. The method of computing dosage in body surface area has not been universally accepted as more accurate and has therefore not been used in this paper.

Digitalis leaf. Digitalis folia is still a very effective drug and is distributed widely under a variety of names. Digalen, Digitan, Digitol, Digifolin, Digitora, Digiglusin, and Digicardium are all synonyms for the digitalis whole leaf. The total recommended digitalizing dose is 15 mg. per pound for the infant and 10 mg. per pound for the child. The recommended maintenance dose is one-tenth the total digitalizing dose. In addition to the whole leaf in tablet form, there is a standard tincture which has the equivalent strength of 10 per cent of the whole leaf.

Glycosides. There are many types of glycosides now available, most of which can be assayed biochemically. One disadvantage in their use is the remarkably small total dosage for children (generally only about one-one thousandth that of the digitalis whole leaf). Thus errors in compounding or dispensing may be disastrous. With the purified glycosides, nausea, vomiting, and diarrhea as symptoms of digitalis intoxication may not be prominent, if present at all, in the infant and child. This may well be a disadvantage, as the first manifestation of toxicity may be

a serious and unrecognized cardiac arrhythmia. In general, the purified glycosides are virtually insoluble in water, and attempts to dilute them may result in a preparation which is pharmacologically inert unless properly dissolved in an effective diluent such as alcohol or propylene glycol.

Digitoxin. Digitoxin was the first of the glycosides to obtain widespread use. It is distributed under a variety of trade names, Purodigin, Crystodigin, Digitaline Nativelle, and Digisidin. It became very popular chiefly because it has almost identical absorption by the gastrointestinal, intramuscular, and intravenous routes. The total digitalizing dose recommended is 0.02 to 0.03 mg. per pound for the infant under the age of 2 years and 0.01 to 0.02 mg. per pound for the child from 2 to 12 years, with essentially the same dosage for all routes of administration. It is slowly, but almost completely, absorbed by the gastrointestinal tract. The initial effect occurs in approximately 2 hours following oral administration and in 30 minutes following intravenous injection. The full effect is reached in from 2 to 9 hours. The duration of effect is approximately 21 days, and the maximal duration of toxicity may be as high as 21 days. It is dissipated as slowly as is the digitalis whole leaf. At the present time, only one digitoxin preparation is available for oral pediatric administration: a stable hydroalcoholic solution of Digitaline Nativelle, each drop of which provides 0.02 mg. of digitoxin. Others are now undergoing trial and may soon be available, however.

Gitalin. Gitalin is manufactured under the name of Gitaligin and is considered to be an amorphous mixture of glycosides. Its great advantage, based on reports, is that the difference between the therapeutic and toxic dose is one-third greater than that of any of the other digitalis preparations.[7] The recommended total digitalizing dose is 0.05 mg. per pound for the infant or child, given orally. The recommended intravenous dose is similar to that of the oral dose, as the absorption is stated to be 100 per cent in the gastrointestinal tract. There is no recorded experience of intravenous administration in the pediatric age group, however. The maintenance dose is one-tenth to one-fifth of the total digitalizing dose. It shows an initial effect in 1 hour when administered intravenously and in 2 to 4 hours when given orally, with the full effect in 6 to 8 hours. The duration of effect is from 7 to 10 days, and the maximal duration of toxicity is from 3 to 7 days. For children, there is a preparation of Gitaligin drops which is a relatively pleasant tasting and stable preparation; each dropperful contains 0.5 mg. of the drug and each 2 drops is equal to 0.05 mg. It is dispensed with a standardized calibrated dropper which gives from 0.05 to 0.5 mg. Gitaligin may be effective when other digitalis preparations are not.[8]

Lanatoside C or D. Lanatoside C or D is known by the trade name of Cedilanid or Cedilanid D. Because of its rapid onset of action, it has been widely used in intravenous or intramuscular doses for the treatment of the supraventricular arrhythmias. Its absorption is poor and irregular by the oral route, and some other preparation is usually substituted for maintenance. The total digitalizing dose recommended is 0.01 to 0.02 mg. per pound for the infant, intramuscularly or intravenously, and 0.008 to 0.01 mg. per pound for the child. Its action is very rapid, with an initial effect in 7 to 9 minutes and full effect in 2 to 3 hours. The duration of effect is 2 to 3 days, and the maximal duration of toxicity is 1 day.

Digoxin (Lanoxin). Digoxin, or Lanoxin, is a purified glycoside derived only from *Digitalis lanata*. It is formed by the degradation of lanatoside C. It is recommended in a total digitalizing dose of 0.03 to 0.04 mg. per pound, given orally, for the infant and 0.02 to 0.03 mg. per pound, given orally for the child. The intravenous and intramuscular doses are 0.02 to 0.03 mg. per pound for the infant and 0.01 to 0.02 mg. per pound for the child, a ratio of about 2:3 between parenteral and oral doses.[9] Its action is quickly manifest; the initial effect is evident in 3 to 8 minutes by the intravenous route and in 2 hours by the oral or intramuscular route. It reaches its full effect in 2 to 3 hours intra-

venously and 6 to 8 hours orally or intramuscularly. The duration of effect is from 4 to 7 days. It has a maximal duration of toxicity of 2 days. Approximately 50 per cent is absorbed by the gastrointestinal tract. It is rapidly eliminated and usually requires a higher maintenance dose than do some of the other glycosides. The maintenance dose is from 20 to 40 per cent of the total digitalizing dose, with an average of 25 per cent.[10] There has been some evidence that Lanoxin may exert a diuretic effect on the kidneys separate from its action on the heart.[11] It is dispensed in a dropper bottle with a calibrated dropper, with each cubic centimeter containing 0.05 mg. of Lanoxin and each 0.2 c.c. containing 0.01 mg. of the drug. There is a great advantage in having a preparation with a standardized calibrated dropper since many errors in dispensing are markedly reduced. There is some relief in knowing that when a prescription is written for a drug with a very small therapeutic to toxic ratio and a very small dose, the medication will be dispensed in a standard dropper which will not vary with each refill of the prescription and which is so standardized that both parents and physician are aware of the exact amount that is being administered.

Acetyl digitoxin. Acetyl digitoxin represents a degradation product of lanatoside A. The trade name is Acylanid. The dosage is essentially the same as that of digitoxin, but its speed of action is approximately halfway between that of digoxin and digitoxin. It may, therefore, represent an important addition when a drug with such an action time is needed. The oral preparation is available as Acylanid solution, each cubic centimeter containing 0.5 mg. and 35 drops equaling 1 c.c. A parenteral preparation is not available at the present time.

Other cardiotonic drugs. Ouabain and acetyl strophanthidin are remarkably rapid acting, digitalis-like preparations when given intravenously.

ADMINISTRATION OF DIGITALIS

Before administering a preparation of digitalis, it should be definitely established that the drug is needed and that either an arrhythmia therapeutically responsive to digitalis or congestive failure is indeed present. Do not treat anoxia with digitalis.

Because of the necessity for close observation, digitalization should preferably be done in a hospital. An electrocardiogram should always be taken, regardless of the time of day or night, prior to the administration of digitalis so that a differentiation can be made between changes due to the drug and changes which are inherent in the condition itself.

The intramuscular route is probably the best method of initiating digitalization. It is impossible to tell whether an infant has taken and absorbed a prescribed amount of the drug orally, particularly when vomiting occurs. The maintenance dose may be continued by oral administration approximately 12 hours after full digitalization and after the cessation of any vomiting.

The glycosides may be given at intervals of approximately 6 to 8 hours. A method of giving one-half the total digitalizing dose at once, followed by one-quarter of the dose in 6 to 8 hours and another one-quarter dose in another 6 to 8 hours, has been found to be practical, provided the apical pulse is checked for any evidence of irregularity or an electrocardiogram is taken between the second and third doses and prior to further administration at any suspicion of toxicity. If there seems to be no marked effect after the calculated dose has been given, another one-quarter of the total digitalizing dose may be given in 6 to 8 hours and prior to institution of maintenance therapy approximately 12 hours thereafter. The choice of using either 6 or 8 hours is mentioned so that the intern does not have to get up at 4 A.M. to check the apical pulse of an infant prior to the next dose of digitalis, when it would probably be safe to wait for another 2 hours if this time interval is more convenient.

In the newborn infant where both hepatic and renal functions are not optimal, it is necessary to guard against intoxication, and possibly the lowest suggested dose should be used.

The "escape phenomenon" may occur in

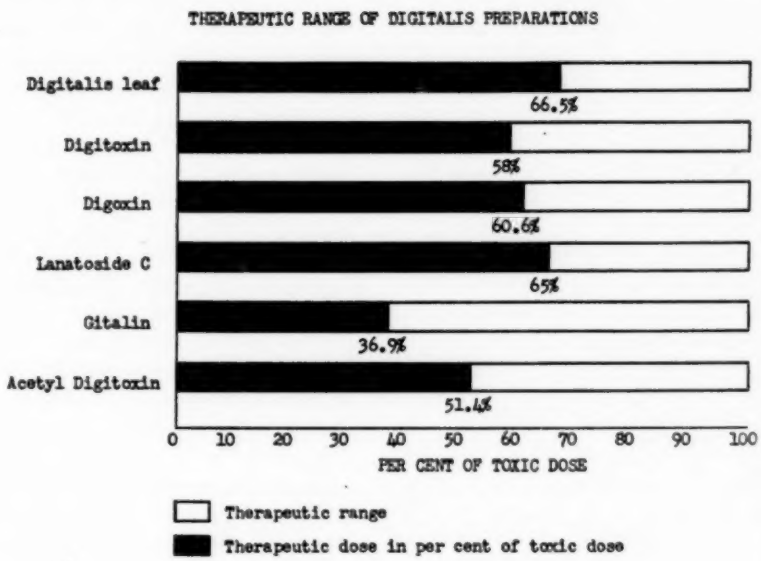


Fig. 1.

the administration of digitalis to infants. Increase in weight may make an initially adequate maintenance dose inadequate. The dosage should be increased as the infant's weight increases, provided digitalis administration is still necessary.

DIGITALIS INTOXICATION

The danger of digitalis toxicity must be emphasized because the ratio between the therapeutic and the toxic doses is smaller than that found in almost any other drug (Fig. 1). The primary cause of digitalis intoxication is overdosage. Most cases of serious digitalis toxicity can be avoided if it is remembered that they can occur at different dosage levels in different patients and that toxicity may even occur in the same patient at different times at the same dosage.

Digitalis intoxication may be precipitated by a loss of potassium. Relatively small doses of digitalis will exert a toxic effect on the myocardium in the presence of hypokalemia which may not be reflected by a low serum potassium value.[12] For this reason, extreme care must be used in administering digitalis to patients who are also receiving diuretics or steroids, who have diarrhea, or who are vomiting.[13] Those with conditions associated with myocarditis, such as rheumatic fever or sickle cell disease, may show evidences of toxicity on a comparatively low dose of digitalis.

RECOGNITION OF INTOXICATION

When purified glycosides are used in infants and children, many of the early symptoms usually associated with toxicity, such as nausea, vomiting, or diarrhea, may be minimal if present at all. Any variation in rhythm during administration should warrant a rhythm strip on the electrocardiogram, usually limb Lead II, to rule out one of the arrhythmias caused by digitalis.

All types of arrhythmias may occur, not only the bigeminal rhythm or ventricular ectopic beats, but also paroxysmal atrial tachycardia with block, nodal tachycardia, and A-V dissociation.[14] Tachycardia or even bradycardia may be evidence of digitalis intoxication, and it could be catastrophic to administer more digitalis on the assumption that the tachycardia or the slow pulse is due to inadequate amounts. Congestive failure itself may be the result of overdigitalization. Do not give more digitalis if in doubt.

The acetyl strophanthidin test for over- or underdigitalization is too hazardous for use in the pediatric age group.

In addition to the arrhythmias there are many obscure signs and symptoms of toxicity which may pass unnoticed, such as headache, vertigo, fatigue, depression, and even urticaria and eosinophilia.

The electrocardiographic signs of T wave inversion, S-T segment depression, and the slightly prolonged P-R interval are not necessarily evidence of digitalis intoxication or even of therapeutic effect.[15]

TREATMENT OF DIGITALIS INTOXICATION

The most effective way of terminating digitalis intoxication is to discontinue the digitalis for a period of time, possibly resuming it with a lower dose after evidence of intoxication disappears. In many cases this may be all that is necessary.

In the presence of severe or persistent digitalis intoxication, the administration of potassium is indicated,[16, 17] either as potassium chloride, 1 Gm. in orange juice every 8 hours, or as Potassium Triplex, 1 teaspoonful (5 mEq. per teaspoon) 3 times daily. In desperate cases with severe intoxication associated with vomiting, the intravenous administration of 40 mEq. of potassium chloride in 500 c.c. of dextrose with water may be indicated, under constant electrocardiographic monitoring, over a period of one hour and not exceeding 1 mEq. per pound as a total dose. It should be given slowly until the arrhythmia disappears or there is peaking of the T waves. Potassium should not be administered if the urinary output is not adequate.

Procaine amide has also been used to treat the arrhythmias of digitalis intoxication in a dosage of 7 mg. per pound orally every 6 hours.

OTHER MEASURES IN TREATMENT OF CONGESTIVE FAILURE

Despite the remarkable action of digitalis, it should not be relied on exclusively for the relief of severe cardiac failure or even arrhythmia. It is better to use calculated therapeutic doses of digitalis and turn to other supplementary measures than to administer the drug until such time as one is confused between adequate and excess digitalization.

In the treatment of arrhythmias, if an apparently adequate dose of digitalis has not converted an arrhythmia, such as paroxysmal atrial tachycardia, the administration of a small dose of quinidine, 3 mg. per pound every 6 hours by mouth, or procaine amide (Pronestyl) 7 mg. per pound every 6 hours by mouth, may be all that is necessary to complete the converison after only 1 or 2 doses.

In the treatment of congestive failure adjunctive measures, such as the following, should be utilized:

1. There should be a thorough search for and treatment of any precipitating cause, such as an infection, for which an antimicrobial agent is indicated, a severe anemia for which packed red cells may be indicated, a metabolic disease, such as thyrotoxicosis or hypothyroidism, or a surgically correctible cardiac lesion.

2. Rest and sedation are necessary adjuncts in treatment, and, particularly in left-sided failure, morphine sulfate, 1 mg. per 10 pounds of body weight, may be helpful. It is usually administered intramuscularly, although it may be given intravenously or orally in the same dosage.

3. Oxygen in a concentration of approximately 40 to 50 per cent may be administered.

4. The use of a low salt diet and either a powdered low-sodium milk or one of the canned or fresh preparations, which are now easily available, should probably be started at the same time digitalis therapy is instituted and may be either modified or discontinued as compensation takes place.

5. Diuretics may be used with caution. The following are effective diuretics, provided one is aware of the danger of a severe electrolyte loss resulting in digitalis toxicity with their persistent use: (a) Mercaptomerin (Thiomerin), 0.1 c.c. as a test dose, followed

by 0.125 c.c. in infants up to the age of 1 month, one-fourth c.c. from 1 month to 2 years, and one-half c.c. to 1 c.c. from 2 years of age up, may be administered every other day intramuscularly or subcutaneously; (b) Chlorothiazide (Diuril) may be administered orally, with 5 to 10 mg. per pound daily as an average dose for children; (c) Acetazoleamide (Diamox) may be given in a dose of 2 mg. per pound orally every day or every other day.

6. Steroids have been recommended for some types of congestive failure, particularly those due to severe rheumatic carditis. It should be stressed, however, that steroids in themselves may cause heart failure and should be used only in the more severe conditions and then with extreme caution.

7. The orthopneic position may give some relief, and in infancy may be simulated by placing the infant over the mother's shoulder.

8. Phlebotomy is rarely indicated in heart failure in infants but may be utilized in older children with severe polycythemia.

9. Left-sided heart failure, rarely identified in infants, may respond to oxygen bubbled through 20 to 30 per cent alcohol for 10 minutes every 30 minutes,[18] administered by intermittent positive pressure mask.

10. Aminophylline in a dosage of 1 mg. per pound, well-diluted and given intravenously with caution, may offer some help in left-sided failure when other measures have not been effective.

CONCLUSION

Digitalis administration represents the best single therapeutic method for the control of heart failure and many of the arrhythmias in infants and children. It is also a drug of remarkably high toxicity with overdosage. The choice of preparation is not as important as a knowledge of the variations of the preparation used and of their therapeutic as well as toxic manifestations.

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Practices and pitfalls in the early detection and control of heart disease in children

John P. Hubbard, M.D.

PHILADELPHIA, PA.

AT THE present time we are able to do far more than ever before to prevent and to control heart disease in children. Twenty years ago, the average annual death rate for diseases of the heart in children 5 to 9 years of age, the age group most susceptible to rheumatic fever and rheumatic heart disease, was approximately 8 per 100,000 in the United States. In 1953, this rate had fallen to 1.5.[1]

Two factors have been especially important in bringing about the gains that have been made over heart disease in this age group. Surgical procedures first became an effective means of repairing congenital malformations of the heart 20 years ago. In 1938, the first successful ligation of the patent ductus arteriosus opened the door to the extraordinary advances in surgical techniques for the repair of cardiac defects.[2] Second, at about the same time, chemotherapy with sulfonamide drugs provided a method of preventing the recurrences of rheumatic fever which so frequently caused death or disability for the child who had once had an attack of rheumatic fever or rheumatic heart disease. Shortly thereafter, during World War II, penicillin became available and was shown to be a means of preventing the initial attack of rheumatic fever as well as a superior method of preventing the recurrences.

These, then, are the three important ways by which we may fight death and disability from heart disease in children: (1) prevention of the initial attack of rheumatic fever, (2) if primary prevention has failed and an attack of rheumatic fever has occurred, then secondary prevention to prevent recurrences of the disease, and (3) surgical repair of congenital malformations of the heart. Knowledge of the proper and effective use of these methods forms the basis of the many and varied practices and programs conducted by individual physicians and by community health and welfare agencies for the prevention and control of heart disease among children. It is timely to review these practices and programs, giving special attention to some of the pitfalls which lie in the path of the unwary.

From the Department of Public Health and Preventive Medicine, University of Pennsylvania School of Medicine, Philadelphia, Pa.

Lecture delivered at the University of Alberta, Edmonton, Canada, under the sponsorship of the program of the Journal of Pediatrics Educational Foundation.

PRIMARY PREVENTION OF RHEUMATIC FEVER AND RHEUMATIC HEART DISEASE

Let us first turn to primary prevention of rheumatic fever, that is, to the prevention of the first attack of rheumatic fever.

Table I. Attack rates of rheumatic fever following epidemic streptococcal infection

Location	*Year*	*Streptococcal infection*		*Rheumatic fever*	
		Source	*Number*	*Number*	*Per cent*
Denmark[3]	1926	Milk-borne	840	30	3.6
North Carolina[4]	1943	Food-borne	100	3	3.0
Boston[5]	1950	Scarlet fever	102	4	3.9
Wyoming[6]	1949 to 1951	Tonsillitis	1,206	32	2.6

Although there is much that we still do not know about the cause of rheumatic fever, it is well established that the disease develops following an infection with the beta hemolytic streptococcus. The evidence comes from many sources. An early and classic study is that reported by Thorwald Madsen[3] from Denmark in 1926. In a small community during the course of about a month, 840 cases of severe sore throat occurred in a milk-borne epidemic thought to be a result of hemolytic streptococcus. In 30 (3.6 per cent) of these cases, rheumatic fever developed 1 to 5 weeks after the onset of the sore throats. Other more recent epidemics of streptococcal infections, followed by similar rates of attack, have been reported from widely separated areas (Table I).

With the advent of antistreptococcal drugs the question naturally arose: Can streptococcal infections be controlled, and can rheumatic fever be prevented in the large group of some 3 out of every 100 persons who develop streptococcal infections? Evidence has now accumulated to indicate beyond any reasonable doubt that, within carefully controlled circumstances, this unfavorable sequence of events can be interrupted.

Rammelkamp and his associates,[6] in excellent epidemiologic studies at Warren Air Force Base in Wyoming during the years 1949 to 1951, demonstrated that prompt and continued treatment of streptococcal infections of the throat may eliminate the streptococcus from the throat and thus may reduce by 96 per cent the clinical manifestations of rheumatic fever which follow streptococcal infections. In this Air Force training base, 798 individuals with streptococcal infections were treated with penicillin promptly and continually for a period of 10 days from the onset of the infection; only 2 individuals developed definite evidence of rheumatic fever. A control group of 804 persons with streptococcal infections were not treated with penicillin; in this group, 17 had attacks of rheumatic fever.

These results were obtained from a captive population in a military establishment where the risk of epidemic transmission of infectious disease is considerable, and in which, under military management, infection may be subjected to well-controlled study and effectively organized treatment.

Can similar results be obtained in the general population? Should a physician, whenever he sees a patient with an upper respiratory infection, which may be due to the streptococcus, immediately administer penicillin? The streptococcal infection itself may be relatively unimportant. But the risk of serious sequelae is high, and we have evidence that they can be prevented. If the physician starts therapy with the intention of preventing these sequelae, he must—if he follows the recommendation of the American Heart Association*—continue treatment for a minimum of 7 to 10 days to achieve his purpose. More particularly, can children,

*The specific treatment schedule recommended by the American Heart Association is one of the following[2]:

1. Benzathine penicillin G.: one intramuscular injection of 600,000 to 900,000 units for children and one intramuscular injection of 900,000 to 1,200,000 units for adults.

2. Procaine penicillin with aluminum monostearate in oil: one intramuscular injection of 300,000 units every third day for 3 doses; double this dose for adults (600,000 units every third day for 3 doses).

3. Oral penicillin: for both children and adults, 200,000 to 250,000 units 3 times a day for a full 10 days. Therapy must be continued for the entire 10 days even though the temperature returns to normal and the patient is asymptomatic.

Table II. Per cent of children with one or more positive cultures of beta hemolytic streptococci in 3 Philadelphia schools during the school year 1956 to 1957

		Number	*Positive (per cent)*
School	A	248	48
School	B	385	57
School	C	454	68
Total		1,087	58

who are most vulnerable to rheumatic fever, be protected in a manner similar to that found to be effective in military groups? How far should we press preventive measures? Should penicillin be given to all children with respiratory infections, or only to those with infections proved to be of streptococcal origin?

In an effort to find realistic answers to these practical problems, a study was undertaken in a school population in Philadelphia beginning in 1955.[8] The object of this study was to determine the incidence of streptococcal infections in this vulnerable age group and also to find out how many children might be harboring streptococci without any manifest signs or symptoms of infection, that is, to discover the prevalence of streptococcus carriers.

Three schools were carefully selected to furnish a population of 1,000 children for study. During the school year, clinical, epidemiologic, and bacteriologic data were obtained from the children and, where indicated, from members of their families. These data have been studied to determine: (1) the carrier rate of beta hemolytic streptococci, (2) the rate of clinically manifested streptococcal infection, and (3) the effect of various treatment programs on both the carrier rate and the rate of clinically manifested infection in the population studied.

The most significant results of this study, which has now continued for 4 years, are the data which show the incidence of positive streptococcal cultures resulting from routine monthly throat swabs of apparently healthy children in these 3 schools. During each of the years of the study, approximately one-half of the children in the 3 schools had beta hemolytic streptococci in their throats at some time during the year (Table II). Positive cultures were found in the throats of from 7 to 29 per cent of the children monthly. Thus we may say the monthly carrier rate for these children is from 7 to 29 per cent and the cumulative carrier rate for the school year is approximately 50 per cent.

The incidence of clinically manifested respiratory infection accompanied by positive cultures has remained relatively low throughout the study and has been independent of the existing carrier rates or the treatment programs which were instituted for purposes of comparison. Even in the group with positive cultures, most of the children had symptoms of undifferentiated respiratory tract illness.

Similar observations have been made in widely separated sections of the United States, suggesting that streptococci in the throats of children may be more frequent than has been suspected. Quinn and his associates,[9] reporting from Nashville, Tenn., found carrier rates for hemolytic streptococci among school children considerably higher than in our schools. Their cumulative carrier rate for the school year ranged from 57 per cent to 88 per cent. From Miami, Florida, Streitfeld and Saslaw[10] have reported a 36 per cent carrier rate. Similar figures have been reported from San Francisco by Rantz[11] and from England by Holmes and Williams.[12]

These observations have a direct bearing upon community programs for the prevention of the primary attack of rheumatic fever and bring to light the first pitfall in detection and control of the infection.

In 1950, Bunn and Bennett[13] initiated a program in Youngstown, Ohio, designed to discover and to treat all streptococcal infections found in school children. A public health nurse obtained cultures from the throats of children who complained, either in the school or at home, of sore throats

or who showed other symptoms of upper respiratory infection. If the throat culture was positive for beta hemolytic streptococcus, penicillin was recommended in full therapeutic dosage. Similar programs, with some variation from community to community, have developed with the support of local heart associations and other local health agencies.

If, however, so many apparently healthy children have streptococcus in their throats with no evidence of infection, 50 per cent in Philadelphia, 90 per cent in Tennessee, and 36 per cent in Florida, should all these children be given large doses of penicillin for the recommended 10-day period? Penicillin is not without some danger; in some cases it may cause drug reactions. Fortunately, reactions are few and usually mild, but they do occur and sometimes may be severe. We do not, therefore, have a completely harmless drug; we must weigh the importance of giving the drug against the dangers of not giving it.

As a result of the accumulated evidence, such as that cited here, we may question the efficacy of those programs which are based upon mass cultures from the throats of school children and upon penicillin treatment for the children found to harbor streptococci. We feel that a far better approach is to place the situation where it properly belongs, in the hands of the family physician, relying upon him to determine whether any child with a severe cold, sore throat, or tonsillitis may have an infection due to the streptococcus. It then becomes the further responsibility of the family physician to decide upon the course of penicillin treatment.

PRIMARY PREVENTION OF CONGENITAL HEART MALFORMATIONS

Before leaving the subject of primary prevention of heart disease in children, mention may be made of primary prevention of congenital malformations of the heart. Here we are in a very limited position. We know that rubella contracted by a woman in the first trimester of pregnancy may be followed by congenital defects in the infant. The risk of congenital defects of the heart and great vessels has been estimated at about 20 per cent.[14] This knowledge leads to the hope that some method may be found to induce rubella or to produce active immunity in girls before the childbearing age. For the present, passive immunity may be induced by immune globulin administered to the pregnant mother known to be exposed to rubella. Other than this, primary prevention of congenital cardiac defects is not susceptible to public health measures. Decision as to whether or not to interrupt a rubella-complicated pregnancy remains a decision to be made by the individual patient and the physician.

SECONDARY PREVENTION

Let us then turn to secondary prevention, to the situation in which primary prevention has failed and the aim is to avoid the unfavorable sequelae of rheumatic fever, rheumatic heart disease, or congenital heart disease.

We are now back in an area where public health measures and community programs are available. These public programs have one element in common: the identification of the vulnerable individual. For the child with a congenital cardiac defect, it is important that his condition be known and that he be under medical observation so that surgical repair may be undertaken when deemed advisable. It is important that the child who has once had rheumatic fever or rheumatic heart disease be continually under medical care so that he may have continuous *prophylactic* treatment to prevent recurrence of the disease.*

Again, we are confronted by pitfalls born of the specific challenge to find the vulner-

*The prophylactic treatment recommended by the American Heart Association for the prevention of recurrences is one of the following[9]: (1) benzathine penicillin G., 1,200,000 units intramuscularly once a month, (2) sulfadiazine, 0.5 to 1.0 Gm. orally once a day, or (3) penicillin, 200,000 to 250,000 units orally once or twice a day, twice daily probably being more effective.

able child and to bring him under proper medical care.

Experience with the school children of Philadelphia provides additional help in the solution of this problem. In Philadelphia, in conformity with state law, all school children are required to have a physical examination upon first admission to school and at periodic intervals thereafter. These examinations are, for the most part, conducted in the school by a school doctor. It often happens that the school doctors are internists or general practitioners who are not altogether familiar with the physical examination of children. To such physicians, a heart murmur is a dangerous sign. Too often they do not realize that a large proportion of normal, healthy children have functional or innocent murmurs which have no pathologic significance. It is not surprising, therefore, that the conscientious school doctor, upon hearing a murmur, takes advantage of available referral to an established cardiac clinic for definitive diagnosis of these murmurs. In the Philadelphia system these children were considered to be "cardiac suspects." At the clinic, both the child and his mother cannot help but be impressed with the attention that is being given to the examination of the heart. Very likely the child is made to stand in front of a fluoroscopic machine in a dark room which may scare him; perhaps also he has a blood sample taken from his arm which hurts him. At last, when all this is over, the doctor may say with a happy smile, "Don't worry, Mother, your child has one of these murmurs which we call functional, and it is no cause for concern." The mother does not know what functional means, but the chances are that she does know what murmur means. This, to her, and perhaps also to her child, indicates a leaking valve and implies heart disease. The mother cannot avoid the idea that her child should be handled with special care and perhaps restricted in his activities. Too many children have developed cardiac neuroses from such procedures and others have actually been turned into cardiac invalids.[15]

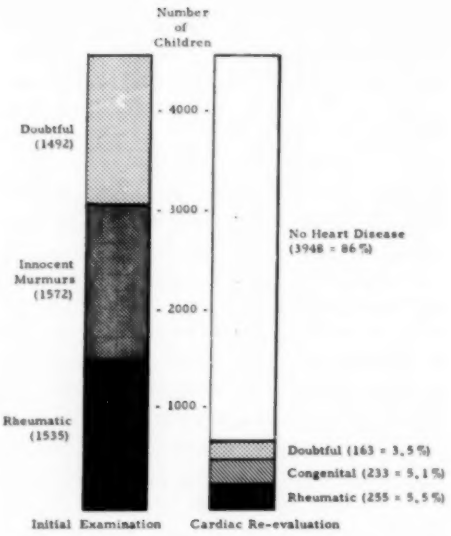

Fig. 1. Results of cardiac re-evaluation of 4,599 Philadelphia school children from 1951 to 1955. (Adapted from the data of Friedman and Wells.[16])

To attack this problem, a so-called secondary screening program was initiated in the school system of Philadelphia.[16] Any child found to have a heart murmur during the school examination is seen again by appointment in familiar grounds at the school by a cardiac consultant or a pediatrician who is familiar with pediatric cardiology and the fact that normal children have innocent murmurs that may be looked upon as normal heart sounds and that are not indicative of any disease or trouble. When this program was first instituted in Philadelphia, it was found that 86 per cent of the children in whom heart murmurs were heard in the first school examination were, as a result of the secondary screening procedure, found to have normal, healthy hearts (Fig. 1). Consequently, for approximately 4,000 children in school during the period 1951 to 1955, anxieties and fears were avoided which otherwise might have resulted from referral to a cardiac clinic. Only 14 per cent of the children found to have heart murmurs were considered to

warrant further study and investigation in a cardiac clinic. This type of program is preventive medicine in a very real sense.

We have gone one step further in our efforts to develop effective methods of early detection of heart disease among school children, while at the same time avoiding the pitfalls of overenthusiasm and overdiagnosis.[17] This further step, as described below, also bears upon the school health examination.

It is important to remember that the school health examination is a screening procedure, limited to the purpose of finding those children who have some signs or symptoms of disease or defect. This is as far as this examination is generally supposed to go. For those who are found to have some evidence of trouble, further procedures are indicated. Definitive diagnosis and treatment are appropriately left in the hands of the family's own physician or to the clinic that they attend.

Since, then, the purpose of the school health examination with regard to the heart is to detect evidence of rheumatic fever, of rheumatic heart disease, or of congenital defects, it seemed that it might be very interesting to use the simple device of asking the parents a few specific questions designed to reveal evidence of rheumatic fever or heart disease. A questionnaire was prepared and completed by the parents when the child entered school. It included such questions as: Has your child had any heart trouble? rheumatic fever? joint pains? Information gained from this source could then be compared directly with information obtained from the school doctor's physical examination required for these same children.

The results of this study are not yet complete but the data already collected are most revealing. In a group of approximately 17,000 children entering the first grade at ages 5 to 6, the physical examination showed definite evidence of congenital heart disease in 7 children. But the parents of 4 of these children already knew of the condition. The physical examination procedure, therefore, disclosed only 3 cases of congenital heart disease, evidence for which had not appeared on the questionnaire. Of these three, 1 was diagnosed as an auricular septal defect and 2 as ventricular septal defects. With regard to rheumatic heart disease, the physical examination confirmed organic mitral insufficiency in 2 children whose parents already knew of the heart trouble. This group of 5- and 6-year-olds, is somewhat young for rheumatic heart disease as the greatest incidence is found among 7- to 9-year-olds. Nevertheless, 2 cases among 17,000 children, a rate of 1.1 per 10,000 is less than expected. Combining the cases of congenital and rheumatic heart diseases, the number of all forms of heart disease is 9 for the total group or a rate of 5.3 per 10,000.

Just what is accomplished by the time, effort, and money expended in the physical examination of the heart in the traditional school health examination? If one assumes that palpation, percussion, and auscultation of the child's heart can be accomplished in 5 minutes in the screening procedure of the school health examination, a little arithmetic indicates that about 1,400 doctor hours were spent in the pursuit of heart trouble among these 17,000 children. The monetary value can then be assessed at whatever hourly rate of pay may be considered appropriate for the services of the school doctor. And this does not take into consideration the time of the school nurse who customarily is in attendance at the examination.

If the procedure yielded important results, certainly one would not wish to measure its value in any such mercenary manner. But does it yield important results? Among 17,000 school children, 3 cases of congenital heart disease were discovered: 1 auricular septal defect and 2 ventricular septal defects. Having made this discovery, the conditions were not such as to require any change whatever in the activities of these children. It could even be suggested that these children might be better off without the knowledge of their cardiac defects and the resulting danger of cardiac neurosis.

The question may, therefore, be asked,

although it borders on medical heresy, if auscultation of the chest in the screening procedure of the school health examination should be discontinued in favor of information obtained from the parents. The evidence suggests the latter course.

These then are some of the responsibilities which advancing knowledge of preventive medicine places upon the practicing physician and upon public health agencies. Here too are some of the pitfalls that may result from overdiagnosis and from overenthusiasm in the control of heart disease in children.

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CLINICAL PATHOLOGICAL CONFERENCE

THE CHILDREN'S MEDICAL CENTER, BOSTON, MASS.

Sidney Farber, M.D., Editor
Gordon F. Vawter, M.D., Assistant Editor

THIS 6 pound, 9 ounce male infant was admitted at 14 hours of age because of marked abdominal distention and green vomitus, present since shortly after birth. He was born after a normal pregnancy with uncomplicated delivery.

One previous pregnancy had produced a girl, now 1½ years of age, with cystic fibrosis of the pancreas. Apparently because of this history, the mother received a special diet throughout her pregnancy.

On admission, vital signs were: temperature 97.6° F. (axillary), respirations 60 per minute, and pulse 148 per minute. The abdomen was markedly distended with purplish discoloration to the right of the umbilicus. There was marked respiratory distress, presumably secondary to great abdominal distention, with grunting respirations. Though the abdomen was quite tense, there were palpable loops of intestine.

On admission the hemoglobin was 16.9 Gm. per cent and leukocytes were 59,200 per cubic millimeter of blood. A urine specimen was unremarkable. Roentgen examination of the chest and abdomen showed fluid levels in a few loops of bowel in the left upper quadrant, no gas elsewhere, and a granular appearance with streaks of density suggesting calcification.

On the first hospital day, during laparotomy, the surgeon found extensive fibrous adhesions throughout the entire abdomen with great thickening of the peritoneum and of the serosa of the intestines. There was no free fluid. Much of the distal small bowel was a matted mass of loops which could not be dissected apart without undue trauma, and the contained stool was puttylike to palpation. Accordingly, a loop ileostomy was performed at a point where the intestine was free, somewhat proximally. Three days postoperatively the bilirubin was 7.2 mg. per cent direct and 17.2 mg. per cent total; the hemoglobin was 14 Gm. per cent. After a somewhat stormy initial course, the baby began to improve, taking feedings, and stooling through the ileostomy, but only a little mucus was obtained on rectal irrigations.

A second operative procedure was done on the fifteenth hospital day, because, despite administration of Viokase, signs of intestinal obstruction continued, which was confirmed by x-ray study. The child was unable to retain a barium enema. At this time, the previously described mass of matted terminal ileum, part of which was necrotic, was resected; the whole segment measured 34 cm. in length. The meconium contained in the bowel showed 4 plus tryptic activity at 1/120 dilution and contained much albuminlike protein. A Mikulicz double-barrel enterostomy was constructed between a small piece of terminal ileum which remained just above the cecum and a piece of small intestine estimated to be about the mid-small bowel. A spur-crushing clamp was applied soon after this second operative procedure, and a

third operation was performed on the twenty-first hospital day, consisting of an extraperitoneal closure of this ileostomy. A sweat test was performed by iontophoresis at this time.

The child did amazingly well during the next 2 weeks, although weight gain was slow. This latter was thought to be due to a rapid gastrointestinal transit time, which was measured at 30 minutes on one occasion by giving some carmine red dye by mouth and noting the time of its appearance at the anus. The infant was maintained on Kaopectate, a fat-free formula, Viokase added to the formula, and broad-spectrum antibiotics. A streaky infiltration of the lungs was noted during the fourth hospital week, coincident with slight temporary deterioration in his over-all state, but this soon cleared under antibiotic treatment. He was discharged on the forty-seventh hospital day, weighing 5 pounds and 7 ounces.

Followed at periodic intervals, the child has done well over the past 10 months, although weight gain has not been rapid.

DR. SIDNEY FARBER. Today we ask Dr. Harry Shwachman to start the discussion.

DR. HARRY SHWACHMAN.* I think that this is a straightforward but most unusual case and that the surgical service should be congratulated on their success in treating this very sick baby with intestinal obstruction.

Before discussing the intestinal obstruction, I would like to say, too, that this patient has cystic fibrosis and we hope to follow him in our Nutrition Clinic.

DR. GORDON F. VAWTER. This patient and his sister are scheduled to make their first visit to the Nutrition Clinic next week.

DR. SHWACHMAN. The mother was on a special diet which is not specified. A number of investigations have shown that the diet in pregnancy can influence the product considerably. Not only exhausting physical work but also grossly inadequate diets may result in premature labor. Miss Bertha Burke, working in the Harvard School of Public Health with Dr. Harold Stuart and the group at the Boston Lying-in Hospital, has for many years been working on this problem. We asked their advice and help in studying mothers who have previously given birth to children with cystic fibrosis. This was done because Dr. Dorothy Andersen in New York initially had extremely promising results, suggesting apparent protection from cystic fibrosis, in a series of 30 pregnancies in families having known cases of the disease. Since then, many additional families have been studied and we shall look forward to Dr. Andersen's report.

These mothers were given a high-protein diet, plus a very generous allowance of the water and fat soluble vitamins. We tried Dr. Andersen's diet in over 30 families in which a number of children were born with cystic fibrosis. We have reason to believe that if the mother has an adequate diet during pregnancy, her baby has an increased chance to be healthy. The prevention of a genetically determined disease by dietary factors during pregnancy is a concept I find difficult to accept, as much as I would like to do so. However, one can draw on numerous examples of hereditary disease in which dietary manipulations may alleviate some of the symptoms. The most outstanding finding in our study was that many of our mothers have very poor diets during pregnancy as well as at other times, and many of them dislike milk intensely.

To return to this child, everyone suspected intestinal obstruction, perhaps a low obstruction, because of the green vomitus. With duodenal obstruction one would not expect green vomitus or abdominal distention. There were palpable loops of intestine, a finding consistent with intestinal obstruction and suggesting firm content. An elevated white blood cell count may accompany meconium peritonitis.

Perhaps the most useful of all laboratory procedures is an immediate x-ray examination. The x-rays might tell us the level of the obstruction and whether the changes suggest meconium ileus because of the air entrapped in solid material, as Dr. Farber

*Dr. Shwachman is Associate Clinical Professor of Pediatrics, Harvard Medical School at The Children's Medical Center, Boston, Mass.

noted many years ago and which Dr. Neuhauser[1] reported in a paper about 13 years ago.

DR. GEORGE B. C. HARRIS. The first x-ray (Fig. 1) shows a marked degree of abdominal distention. Gas fills the upper loops of the small bowel and there are a few fluid levels present. The rest of the abdomen is quite homogeneously opaque and on the films themselves there are streaks of calcification in the abdomen, indicating meconium peritonitis. There is a little evidence of mixture of the intestinal contents and air in some of these loops but it is not the classical picture of meconium ileus. We now recognize that this particular finding occurs in only 40 to 50 per cent of patients with meconium ileus; the rest of them present with signs of intestinal obstruction. I would suspect that we are dealing with a high intestinal obstruction (only a few loops of small bowel are outlined). The large soft tissue mass suggested in the lower abdomen probably represents a volvulus or a great matted mass of intestine. This is something one would come to recognize from previous experience. Prior to the second operation there is still evidence of a disturbance in motility and one would suspect that there is still some degree of intestinal obstruction. There is very little evidence of pulmonary consolidation.

In the last examination, when the patient was over 1 month of age (Fig. 2) there were multiple air-fluid levels throughout the small bowel indicating a nonspecific disturbance in motility, but nothing to indicate mechanical obstruction at this time. The lungs were quite clear then.

DR. SHWACHMAN. The impressions gained from examination of the x-rays were borne out by the findings at laparotomy. This peritonitis was probably present for a long time, with rupture of the intestines before birth, so that sufficient time had gone by to permit the meconium to become calcified. I do not know exactly how long this went on, but it could have been 1 or 2 months. The bowel contained stool which was puttylike to palpation as is characteristic for meconium ileus.

Fig. 1. X-ray taken on admission. Abdominal distention with a few fluid levels and generalized "ground glass" density with streaked heavier densities are seen.

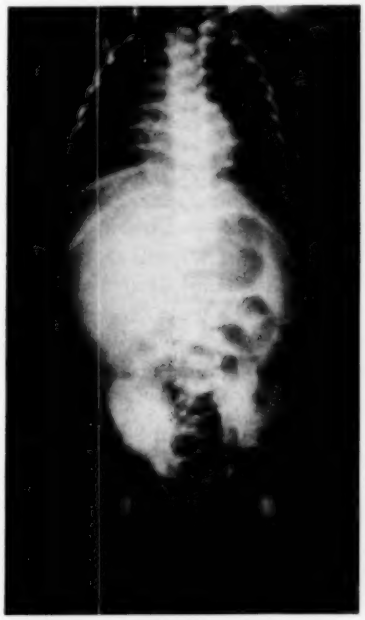

Fig. 2. Final x-ray. Nonspecific disturbance in motility is suggested.

I think many surgeons would feel pretty hopeless when presented with this matted mass of intestine. Dissection is obviously impossible and one would feel that the best thing to do is to relieve the obstruction by loop ileostomy, and hope that the baby would gain sufficient strength to permit a later corrective operation. This is exactly what happened. The jaundice which developed could be a result of a number of factors: immaturity of the liver, peritonitis, or perhaps some infection and associated hemolytic process, but this baby had tremendous vigor and survived this initial stormy course. At the second operation, approximately 2 weeks later, a more definitive procedure was carried out and 34 cm. (or about 15 inches) of intestine had to be removed.

This brings up the question as to how much of the intestine one can remove from a small baby and hope for survival with adequate nutrition and growth. This is not the longest segment that has been removed from a baby without any difficulties later on, in so far as growth is concerned. In the large number of patients with meconium ileus who have been operated on here, as much as 3 feet or more have been taken out and the baby, when subsequently followed, showed no evidence of deficiency of vitamin B_{12} or other factors in growth which could be directly ascribed to inadequate length of small intestine. I feel sure that one can remove as much as half of the small intestine and not necessarily interfere with nutrition and subsequent growth. There may be, as there is in many cases of meconium ileus, vitamin K deficiency. We have come to recognize this as a very important deficiency which can always be prevented by adequate dosage of vitamin K. This is not a long-term nutritional failure as implied by growth failure and the possible lack of hematopoietic factors (folic acid and vitamin B_{12}).

I doubt very much that there were fistulous tracts, despite the slow weight gain and rapid gastrointestinal transit time. I think that we were originally dealing with a meconium ileus that ruptured during intrauterine life, probably with some complicating form of obstructive lesion, such as adhesions, volvulus, or secondary atresia. Dr. Zuelzer[2] reported, in one of his cases of meconium ileus, the occurrence of complete intestinal atresia, in which he thought the granulomatous reaction to meconium and the rupture that had taken place at the site, with subsequent formation of fibrous tissue and scar tissue, ended up as something indistinguishable, grossly, from atresia. It is important to emphasize again that atresia (sometimes multiple) may be a complication of meconium ileus.

The diagnosis of meconium ileus in this patient would be strongly suspected on the basis of the positive family history and the x-ray, although meconium peritonitis with calcification may occur in the absence of cystic fibrosis. The Farber test,[3] based upon the presence of squames in meconium, can be of great help in trying to determine whether one has atresia or not. If one found the epithelial cells distal to the site of obstruction, then one could be sure that this baby had a patent intestinal lumen at one time, and that the obstruction was acquired relatively late, or was "secondary." I expect that Dr. Vawter will tell us that beyond the point of obstruction he found epithelial cells from the vernix. We gave up duodenal intubation as a diagnostic procedure in cases of neonatal intestinal obstruction in 1940 or 1941, since we obtained only a fraction of a cubic centimeter of duodenal fluid after having a duodenal tube in place for about 2 hours. The babies are usually too sick, and I do not believe anyone would advocate this preoperatively.

This type of case is a surgical emergency and we are interested only in opening the abdomen to look around and to do what can be done.

For the past year our group, especially Dr. Ezra F. Elian, has been using the iontophoresis sweat test, and for the past 8 or 9 months we have done sweat tests by this method exclusively. In another case of intestinal obstruction, Dr. Elian has done the iontophoresis sweat test when the baby was

about 10 to 12 hours of age, prior to the surgical procedure. The chloride value of 123 mEq. per liter in 60 mg. of sweat was extremely high. This baby was later operated on and found to have meconium ileus. The sweat electrolytes in our present patient showed a chloride concentration of 109.1 mEq. per liter and a sodium concentration of 83.5 mEq. per liter. However, this test cannot be expected to yield good results in all early cases because in 6 normal babies that he tested at 1 day of age, he was not able to get enough sweat to do an analysis. Perhaps there is a difference in babies with meconium ileus in that they may produce more sweat. This is one of our current problems.

Another diagnostic procedure which may be of some help is the chemical analysis of meconium. The abnormal meconium contains a large amount of serum protein.[4] It constitutes a great percentage of the total protein present. Dr. Green, Dr. Clark, and I presented some chemical experiments with meconium from patients with meconium ileus. We found that, using three different techniques, the chemical precipitation test with 10 to 20 per cent trichloroacetic acid gave a strongly positive reaction from the water extract of the meconium in meconium ileus patients but in normal babies gave no reaction whatsoever. Electrophoresis experiments were carried out with the water extracts of meconium and most of this protein fraction migrated like albumin. Immunologic tests demonstrated that the major fraction in the meconium was albumin. Since normal meconium does not contain albumin, this test can be helpful. Attempting to demonstrate trypsin in the meconium is not very useful because 75 per cent of normal babies have no trypsin in their meconium. This may be a matter of the rapidity with which meconium is passed.

I do not think we should go into the medical treatment of this baby at this time.

Dr. Harris. I would like to return to the point concerning the atresia secondary to the meconium ileus.

In approximately one half of the infants with meconium ileus we can only make a diagnosis, if we are fortunate, of intestinal obstruction. It can simulate obstruction from atresias of the small bowel on a developmental basis or can sometimes perhaps be confused in patients who have infantile Hirschsprung's disease, so that on the basis of the x-ray examination alone we really cannot always make the diagnosis of meconium ileus. We are coming more and more to recognize that patients in whom there is a roentgen appearance suggestive of congenital atresia of the small bowel have a good chance of having an atresia secondary to meconium ileus.

Dr. Farber. Dr. Longino, would you like to say something?

Dr. Luther Longino. Only to agree with Dr. Shwachman on the diagnosis of this case. We are coming to recognize that more children witih meconium ileus have atresia, undoubtedly secondary to perforation during intrauterine life. Those that Dr. Harris says you cannot be positive of, you do not always have to be positive of, since you know the child is in trouble and requires operation as soon as possible. We like to carry out surgical procedures in one or more stages, as was done in this child, not only with meconium ileus but with some cases of atresia. These are not very traumatic procedures, unless there are very marked adhesions, as in this instance, and many operations can and probably ought to be done under local anesthesia, particularly those with meconium ileus. Whether or not the anesthetic gases have anything to do with stirring up pulmonary difficulties later on we do not know, but we would rather do without, if possible. We do a lot of Mikulicz ileostomies, which consist of bringing two loops of bowel up side by side, like a double barrel shotgun, suturing them in this position. The involved bowel can be brought outside the abdomen and then resected. Then a clamp is used to cut off the blood supply gradually, the tissue between the blades of the clamp dies, and the two loops become sealed to each other. It is very easy to do this under local anesthesia. The stoma is closed extraperitoneally and at no time do you contaminate the peritoneum of

the child. These ileostomies are done at the junction of the dilated loop where there is liquid meconium and puttylike material. After the ileostomy we use pancreatic enzyme preparations to help to irrigate the lower loop. As soon as the lower loop of the intestine is opened and irrigated, the ileostomy is closed. We have actually done some ileostomies in the jejunum and have been successful. Usually this means that as soon as the operation is over, you must put on a clamp so as to reduce the time of marked fluid and electrolyte loss. I do not know how much intestine one can remove, or how it was measured in this case. Meaningful measurements of the length of intestinal segments are very difficult, since one can double or triple the length of a loop, depending upon the care with which it is dissected. I doubt if we really did take 34 cm. of bowel in this case; it could be more.

I think that reports from St. Christopher's by Pilling and his associates state that they left anywhere from 6 to 10 inches of small bowel in 2 children. The children had quite a difficult course for a time but they finally were put on a fat-free diet, and are said to be all right at the present time. I just can't answer how much of the small intestine you can take out. I think it varies with the individual.

In the 14 years I have been here, treatment of these babies with meconium ileus has gone through a number of cycles. We have largely abandoned intubation with decompression and irrigation as primary treatment, just as we have given up primary anastomosis after loop resection. I think, looking back to 1947, 1948, and 1949, we might have had one live child out of 8 to 10 of these patients in a year. With our present approach we are reversing these statistics.

DR. SHERWIN KEVY. Is this a little early for the symptoms of meconium ileus to begin?

DR. LONGINO. It is not. We have seen obstruction in these children so bad that there was difficulty in delivery, because of abdominal distention, sometimes with huge volumes of peritoneal fluid.

Fig. 3. Surgical specimen. A tightly coiled mass of intestinal loops is firmly bound by adhesions. In the center of the coil the small gray curled structure represents the site of atresia.

DR. HARRIS. Despite the remarkable success of the present method, there have been later complications and I thought that Dr. Longino would like to say a word about them.

DR. LONGINO. I think that Dr. Harris is speaking of what we here call the "blind loop syndrome." We use the term more broadly than some people. A blind loop or pouch of intestine may be formed by the method of opening the two loops under the clamp. A few of these "blind loops" have been complicated by bleeding later on, or by partial intestinal obstruction. In these cases we have reoperated, resected the blind loop, and have done an end-to-end anastomosis. However, having to do this is better than having no child at all.

A PHYSICIAN. Should we suspect something concerning the baby's liver function on the fourth day of life, when he has a proportionally high direct bilirubin. I know children with cystic fibrosis have cirrhosis, but they are usually older ones. What is the hepatic situation in this case?

DR. SHWACHMAN. We do not know.

DR. VAWTER. Of a series of 8 infants with meconium ileus complicated by actual intes-

tinal atresia, 3 had focal obstructive biliary lesions in the liver at autopsy. This is an unusually high incidence. Unfortunately, these patients did not survive the first few weeks of life. These results parallel those of Dr. Jay Bernstein in Detroit, who noted this in one of 3 similar cases. We wonder whether the liver is peculiarly susceptible to involvement in patients who have this type or severity of meconium ileus. Obstructive biliary lesions seen at this age are sometimes comparable to the characteristic hepatic lesion of older patients with cystic fibrosis.

DR. HARRIS. The Neuhauser sign of mixed gas and meconium suggesting meconium ileus is also seen in infantile Hirschsprung disease, but that is most unusual. Dr. Harvey White observed that most of the patients who have meconium ileus (uncomplicated by volvulus or secondary atresia or peritonitis) will show an absence of fluid levels when the x-ray films are taken in the upright position. Presumably, if you observe these children at an early enough stage, and they have not been given anything by mouth, the secretions of the intestinal tract are sufficiently viscid so that they will not form air-fluid levels. He also pointed out that when the roentgenogram of a patient reveals both the Neuhauser sign of meconium ileus and fluid levels, one can suspect some underlying complication, such as volvulus, with the meconium ileus.

DR. FARBER. Dr. Vawter, will you give the findings in this patient?

DR. VAWTER. This case exemplifies the fact that there can be organic obstruction of the intestine in patients with *meconium ileus*. This patient had three different lesions, potentially accounting for such a complication. The specimen removed at the second operation (Fig. 3) is a tightly coiled, turban-like mass of distended bowel heavily matted together by dense adhesions resulting from *intrauterine rupture of intestine* and, in themselves, capable of causing *obstruction*. Second, there is a *volvulus* which is not rare in meconium ileus, and which probably accounts for the rupture. Third, barely visible

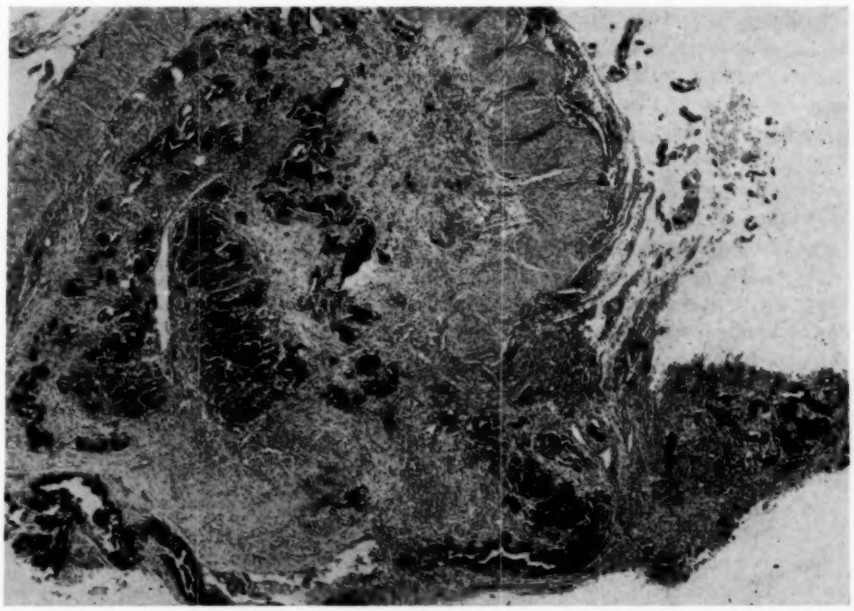

Fig. 4. Microscopic cross-section of site of atresia. Intraluminal, mural, and peritoneal granulomatous response to meconium has become fibrotic and calcified after extensive necrosis. (Toluidine blue-eosin. ×25.)

in the center of the gross specimen is a region of *acquired atresia* which may be the lesion which initiated the volvulus.

As. Dr. Shwachman prophesied, this patient did have squames distal to the site of obstruction, indicating that the squames were present in the meconium some time before the obstruction occurred, perhaps around the fourth month of gestation.

Microscopically, the segments of the bowel show all the classic changes of meconium ileus. It is not hard to visualize how distention, inspissation of secretion, and the presence of meconium may lead to slitlike rupture of the intestinal wall, with dissection in the submucosa to produce a granuloma or eventually lead to ulceration and necrosis of the entire thickness of bowel wall. In the cross section of the bowel through the site of the acquired atresia, a very extensive fibrous peritonitis with the masses of calcific deposit forms around extruded squames and other cellular debris (Fig. 4). The muscular wall of the intestine can be followed part way around until it becomes totally necrotic and calcified. The rest of the submucosa is extensively involved by the meconium granuloma which led to complete obstruction.

Such acquired atresia may be the only obstructive lesion in the intestinal tract apart from the meconium ileus, and may on occasion be multiple. I believe Dr. Gross reported one instance in which there were three separate sites of atresia of this nature in the small intestinal tract, so it behooves one to explore the abdomen carefully and extensively for the possibilities of multiple organic obstructions in such patients.

Concerning the hepatic lesions in these patients, it is a little difficult to be sure of their significance, since they were found in patients who came to autopsy at a very early age, and some may represent an ascending cholangitis, secondary to the peritonitis or to other disease. We should not be surprised if liver involvement ultimately came to be an important part of this patient's disease.

DR. FARBER. Thank you, Dr. Vawter.

Dr. Shwachman, do you have anything to add?

DR SHWACHMAN. Prior to about 1947, most of the babies with meconium ileus who were operated on in this hospital did not survive beyond a few weeks of age, or 1 or 2 months, at the most. In 1947 we had one youngster who spent a number of months in the hospital. He had all the difficulties attending high ileostomy, with tremendous fluid losses and it was touch and go for many weeks. This boy has been followed regularly by us; he must be 12 or 13 years old by now. He attends school regularly and one would never know that there is anything wrong with him at the moment. I think the reason for this is that, once the surgical problem is corrected, the outlook depends entirely on how much pulmonary or hepatic difficulties these children get into. This patient has had no trouble whatsoever.[5]

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COMMENTS ON CURRENT LITERATURE

Psittacosis: exposure to infected turkeys

IN SPITE of broad measures designed for its control in the United States, psittacosis as a clinical disease in the human subject is increasing. According to a report by Scruggs[1] in 1957, the number of reported cases in a single year (1955 to 1956) showed an increase of 90 per cent (278 to 508 cases). This increased incidence of the disease has been due in large measure to the marked increase in the number of psittacine birds being imported into the United States or raised here for use as household pets. The increased incidence involves both children and adults. In some areas of the country, transmission of the disease from domestic fowl is becoming a problem of some importance. During the 4-year period from 1948 to 1952, 5 outbreaks among poultry workers were described with clinical illnesses in 196 persons, 7 of whom died.[2] From 1952 to 1954, a total of nearly 300 cases occurred, primarily among workers whose tasks involve the plucking and dressing of turkeys.[2] The disease in human subjects has been acquired also from other non-psittacine birds including pigeons, ducks, guinea fowl, pheasants, and members of the cuckoo family such as the road runner.

The *American Journal of Medicine* for November, 1959, carried a timely and informative article by Yow, Brennan, Preston, and Levy.[3] This report deals particularly with the pathologic findings of psittacosis and describes 2 cases with liver involvement in addition to the clinical and pathologic findings usually considered characteristic. As the authors point out, the clinical manifestations of this disease vary widely. Recent reports suggest that the incubation period also varies from 1 week to a month or more, depending apparently upon the extent of individual exposure. In epidemics among poultry workers, a short incubation period has characterized the illness in those heavily exposed, as in "plucking rooms." Serologic studies indicate that subclinical infections occur which frequently are unrecognized because of their similarity to the common respiratory diseases. The duration of the illness may be short, terminating abruptly, or may pursue a long, low-grade course for 3 months or more. In infected birds the virus is present in the blood and the tissues and is discharged with regularity in the cloacal contents. Transmission to the human subject is usually by inhalation of dried excreta but may occur also from the handling of infected tissues and in rare instances by bite. While the disease can be transmitted by healthy birds acting as carriers of the psittacosis virus, such cases are mild as a rule. The rate of the attack and the severity of the illness appear to be related to the infective dose. Birds with active infection are more likely to transmit the disease to man than are the asymptomatic carriers. The disease is not transmissible readily from one human subject to another; however, such transmission has been recorded, especially during epidemic periods when there have been family outbreaks. In an epidemic in Louisiana in which 8 deaths occurred, 18 persons acquired the disease directly or indirectly from 1 patient.[4]

The current report by Yow and his associates[3] describes a turkey-borne epidemic in Texas, and is concerned particularly with

the clinical and pathologic findings. A detailed epidemiologic study is reported elsewhere.[5] The usual course in severe infection is that of acute onset of fever with elevation between 103° to 105° F., the temperature remaining high for from 7 to 10 days and declining by lysis during the second or third week of the illness. Characteristically there is relative bradycardia, but in nearly all fatal cases the pulse soon becomes rapid and weak. Severe headache is a consistent feature, with myalgia, nausea, and vomiting variable in severity. Anorexia is a prominent feature of the disease. Little or no diarrhea is noted. The leukocyte count in psittacosis is low, as a rule, but in some instances may be slightly above the normal range. According to these authors, the most helpful laboratory finding with respect to diagnosis is the rising titer of complement-fixing antibodies during the course of clinical recovery. These are usually detectable by the end of the first week of illness. In birds, the primary sites of the disease process are the liver, the spleen, and the pericardium. In the human subject, the lung is involved most consistently, although there have been some patients who showed no clinical or roentgenographic evidence of pneumonia. As in other viral pneumonias, physical findings are not obvious during the first few days of fever. The sputum is scanty but in severe cases increases, especially during the stage of resolution. It is nonpurulent and mucoid in character. The cough is relatively inconspicuous in contrast to the severe cough which is characteristic of other forms of viral pneumonia. While some patients do complain of pain or soreness in the chest, a true pleuritis is rare. In birds, however, the disease is characterized nearly always by polyserositis. Splenomegaly is common in the more seriously ill patient and is apparent about the end of the first week. Signs and symptoms of pulmonary insufficiency are seen only in severe cases. Both experimental and clinical evidence has indicated that the tetracycline group of antibiotics exerts a suppressive effect upon the virus of psittacosis. These antiviral substances are not actually virucidal, however, and therapy must be initiated early and continued for about 3 weeks in order to prevent relapse.

These authors find it surprising that in view of the mortality reported for this disease, so little information concerning its pathology has been recorded. The most profound changes caused by the disease in the human subject are seen in the lungs, but in those patients with the more severe clinical manifestations specific lesions may be seen in profusion in the liver, the spleen, and in a few instances in the brain (leptomeninges). In these respects the pathologic findings seen at autopsy of human subjects closely resemble those associated with the disease in birds. The pulmonary lesion is a lobular interstitial pneumonitis. The affected lung areas become consolidated and their "rubbery gelatinous consistency . . . is almost pathognomonic of the nature of the process."[3] The hilar lymph nodes show a similar inflammatory process, "large numbers of swollen mononuclear macrophages distending the afferent lymphatic sinuses."[3] These hilar lymph node changes are characteristic also of other viral and rickettsial pneumonias. In the spleen the gross and microscopic changes are described as those of acute splenic tumor with mild reticuloendothelial proliferation, and in some instances focal necrosis.

Changes in the liver have been described as those of a "nonspecific reactive hepatitis" with intralobular focal necrosis of liver cells. The degenerating cells are surrounded by hyperchromatic swollen Kupffer cells, occasional lymphocytes and rare polymorphonuclear leukocytes. "Kupffer cell hyperplasia is noted throughout the liver, often with erythrophagocytosis and cytophagocytosis,"[3] and in some instances cellular parasitism of the Kupffer cells by the elementary bodies of the psittacosis virus is apparent. Mononuclear cell increase in the portal tracts and a mild fat accumulation in the liver cells have been noted. The cardiovascular system may be involved to a variable degree; necropsy findings include dilatation of the right side of the heart, hypertrophy of cardiac muscle, cloudy swelling and fatty degeneration of the myocardium, interstitial edema, interstitial

infiltration with plasma cells and lymphocytes, and subendocardial hemorrhages especially in valvular regions. Interstitial myocarditis has been described as a feature of fatal psittacosis in children.[6] Involvement of the kidney is characterized by hyaline glomerular capillary occlusions. Patients report anuria with suprapubic discomfort; in some instances albuminuria is reported to be marked. Involvement of the nervous system has consisted of a "macrophagic and fibrinous or gelatinous arachnoiditis about the Sylvian fissures in the brain and medial portions of the cerebral hemispheres."[3] As a rule, no demyelinization and no neuronal degenerative changes are apparent.

In the current report by Yow and his associates,[3] 24 patients with clinical psittacosis were studied in some detail. Two of the patients hospitalized were gravely ill, and 1 died. Both of these patients showed clinical and laboratory evidence of hepatitis and of altered renal function. While pathologic studies have revealed microscopic evidence of focal necrosis in the liver of patients dying from psittacosis infection, clinical evidence of jaundice has not been reported previously to the authors' knowledge. In the fatal case of these 2 patients presented in detail, the necropsy findings included "bilateral severe interstitial pneumonitis; severe tracheobronchitis; acute segmented 'toxic' nephrosis ('lower nephron nephrosis'); acute non-specific reactive hepatitis; and multiple focal lymphocytic meningitis."[3] Elementary bodies of the type described in psittacosis infection were observed in the lung tissue and within the cytoplasm of mononuclear macrophages. In the opinion of the authors, "the jaundice, acute anuria, central nervous system signs and the severity of the pneumonitis" in these 2 severely ill patients "would strongly favor the generalized nature of psittacosis infection." The importance of early diagnosis and the early initiation of tetracycline therapy is stressed, especially in those instances where definite exposure to the agent is known.

RUSSELL J. BLATTNER

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PEDIATRIC PROFILES

Henry F. Helmholz

(1882—1958)

FROM HIS duty-directed mother, Henry Helmholz derived his perfectionist drive, and from his genial father, the habit of getting along with people. The combination became his rule of living.

"He had set himself the objective of excellence," wrote a Hopkins' classmate, "and whatever he did gives that impression."

Helmholz compressed his undergraduate days at the University of Wisconsin into 3 years. During that time he was awarded letters in both basketball and track and was a tennis champion as well. He so successfully managed his fraternity house that its finances were pulled out of the red. By the time he had graduated from medical school, he had not only been one of the top men of his class but he had won membership in the honorary fraternities of Phi Beta Kappa, Sigma Xi, and Alpha Omega Alpha.

In 1906, the year Henry Helmholz was graduated from Johns Hopkins, Welch and his disciples were laying the groundwork of scientific research in American medical schools. Pathology and bacteriology were then, as chemistry is now, the keystone to the basic understanding of the processes of disease. Osler had begun his career as a pathologist. Whatever the clinical direction of one's interests, pathology was considered the way to medical competence. Henry Helmholz chose that way and spent a year under Welch. The five papers published in the Bulletin of the Johns Hopkins Hospital of 1907 represent his year's work and show the thoroughness and drive which characterized all his activities.

Fig. 1.

Helmholz's interest in pediatrics apparently resulted from his association with Dr. Charles Emerson, who was Resident Physician at Johns Hopkins when Henry was a senior student. Emerson, whose name appears as an author in the pediatric texts of that day, is described as "a person of deep

religious piety." He organized a group of medical students to make "a study of the social and hygienic conditions existing in the homes of the dispensary patients." While we have no knowledge that Helmholz was one of this particular group, his choice of pediatrics, Dr. Samuel Amberg thinks, must have been the result of Emerson's influence.

At the time Henry received his medical degree, pediatrics had barely emerged as a specialty in medicine. The *Archives of Pediatrics* was filled with reports of infectious diseases and problems of feeding. An unusual clinical incident, such as "the third successful operation on pyloric stenosis in America" reported by Howland, occasionally enlivened its pages. The study and prevention of infant mortality were hardly a whimper in the noise of the national scene. (Theodore Roosevelt was President.) Pediatrics was striving for recognition as a specialty. Baginsky, in defense of pediatrics, had just written a spirited reply to Quincke who contended that only during the first few months of infancy did a child need specialized care.

In Germany, however, a galaxy of pediatric investigators was engaged in basic physiologic studies. *Concepts* of disease were taking the place of *case* studies. It was the era of great personalities in European medicine. Heubner's clinic in Berlin, Czerny's in Breslau, and Escherich's in Vienna provided the opportunities for the pediatric frontiersman which Paris provided for the artist.

Helmholz, having completed his Pathology Fellowship under Welch, spent a few months at the Contagious Disease Unit of the Boston City Hospital. Late in December, 1907, he was married to Isabel Lindsay, who had just been graduated from Smith College. They sailed for Germany in January but not before interrupting their honeymoon to spend New Year's with the family.

The young Helmholzes lived in a multinational pension on Charitéstrasse near Heubner's clinic. Here Helmholz obtained an appointment as a volunteer assistant. His fluency in German, which he had acquired as a child from his family, and his training

Fig. 2. Students and teacher in the Department of Pathology at Johns Hopkins Hospital from 1906 to 1907 are (upper row, left to right) Helmholz, Welch, and MacCallum, and (lower row) Fabyan and Whipple.

in pathology stood him in good stead. He was soon engaged in his first pediatric investigation, his oft-quoted observations on "Duodenal Ulcer in Atrophic Infants." At Finkelstein's suggestion, he accepted a service in a Berlin Kinderfürsorgestellung which gave him the background for his subsequent interest in the public health aspects of child welfare.

Later, in Breslau, he was a fellow student of Krasnogorski, the famed Russian pediatrician, who at that time was occupied with his early studies in conditioned reflexes. The 1908 *Jahrbuch für Kinderheilkunde* contains, among other items, publications by each of these men, who had the good fortune to renew their friendship at later international meetings and at Leningrad when the Helmholzes visited him in 1927.

In 1910 Helmholz returned to this country to start pediatric practice in Chicago. Fifty years ago pediatric practice had not reached the inflationary pattern taken as a matter of course by present-day graduates. Pediatrists were few, but parents clamoring for their services were even fewer. Since his consulting room was uninvaded, Helmholz found time to take on the directorship of the newly formed Infant Welfare Society of Chicago as well as to continue investigations in the laboratories of Rush Medical College, investigations prompted by his Berlin studies.

In addition, he soon took a staff appointment at the Children's Memorial Hospital and one at the Sprague Laboratory where Dr. Amberg was director.

Residents and interns who served under Helmholz remember that they had a deep affection and admiration for him—for the kind of person he was, rather than for any startling apocryphal diagnoses so often attributed to favored physicians. They recall his straight figure and brisk stride, as he paced through the hospital corridors, and his considerate and easy manner, mingled at times with a certain detached reserve. He was not "one of the boys." Even as a student and as a fellow member of the Pithotomy Club, a social group of his Baltimore student days, a fellow student wrote, "he lacked the spectacular peccadilos . . . though he was often found giving first aid to fellow members whose enthusiasm for liquid refreshments surpassed their capacity to metabolize what they had ingested."

Neither in his medical rounds nor in his medical writings was he given to dramatic expression. There was an occasional exception as, when on rounds, an intern without telling the child what was about to happen, readied himself for opening a hot drum. The intern could never forget the tennis racket grip of the chief on his arm as he poised the paracentesis knife for its plunge nor the injunction never to inflict pain before first acquainting the child with what he was about to do. Residents found it a special privilege to listen in when Dr. Helmholz counseled with alarmed parents, for they learned the lesson that humaneness needs as much emphasis as methods of diagnosis or modes of therapy.

Helmholz drove in every morning from Evanston with Dr. Louis Sauer, a Sprague Fellow, and later his associate. Except for his rounds, he spent the morning in the Sprague Laboratory.

Here he soon became involved in his indefatigable search for the basic explanation of the urinary infections of childhood. One half of the more than 200 papers he wrote had to do with problems of the urinary tract. His early investigations followed the customary pattern of producing the disease in lower animals and studying the resulting sequences. In his later days at the Mayo Clinic, after a series of carefully contrived investigations of "the kidney as a filter," his approach became pragmatic. During this time he wrote numerous reports on the therapeutic value of each newly discovered antibiotic or urinary antiseptic. Those who encountered him in his public health activities sometimes deplored the undue proportion of time he gave to the urinary tract studies, much of which, in the ever-accelerating pace of medical discovery, seemed headed for obsolescene or the brittle eternity of microfilm shelves.

The Sprague Laboratory of the Children's Hospital served as both a research section and a counseling area for problem cases. The residents, who were automatically Sprague Fellows and actually received their modest pay from the Sprague Laboratory, felt an equal loyalty to hospital and laboratory. This arrangement, plus the quieter atmosphere of the laboratory, brought about a close relationship between the residents and their respective chiefs, Dr. Helmholz and Dr. Amberg.

There were countless acts of kindness and consideration which were done unobtrusively and apparently effortlessly. One of these acts is related here.

I was finishing my senior residency at the Children's Memorial when Dr. Helmholz asked me about future plans. I had not decided whether to accept an instructorship offered by Dr. Sedgwick at Minnesota or whether to return to Georgia. He told me then that Milwaukee was in need of a pediatrician and suggested that I meet him on August 26 at the Pfister Hotel. There, at the appointed time, I found Dr. Helmholz with 3 Milwaukee physicians. After lunch he took me to the office of Dr. Fred Gaenslen, who, upon Dr. Helmholz's request, permitted me the use of the desk of one of his colleagues from 1 to 3 P.M. each day.

After that, in line with his characteristic pattern of thoroughness and kindness, he produced a map of Milwaukee, and pointing

out a section of the city from which he thought calls for a pediatrician might come, suggested that I live in that area. Finally, he asked if I needed money and wrote a check as a loan.

Six weeks later, on a visit to Milwaukee, Dr. Helmholz looked me up and inquired about my practice. I told him that I was enjoying the use of the desk in the office and the opportunity for study, but so far there had been no demand for my services. Two days later came my first call, which took me to the home of a cousin of Dr. Helmholz.

In 1921 Henry Helmholz became Head of the Section of Pediatrics at the Mayo Clinic. His continuing interest in the education of the pediatrician shows itself in his description of his department which was part of the series on "Pediatric Clinics" published by the JOURNAL OF PEDIATRICS. "In our training of the Fellows," he wrote, "we aim principally to prepare men for the care of sick children and for supervision of the growth and development of well children."

He inaugurated the practice of assigning Fellows to visit the children of Rochester in their homes. Roger Kennedy was the first to serve on this assignment which now occupies the time of three Fellows and a Consultant.

Later, he was instrumental in starting the Rochester Child Health and Development Institute, which is described in the Profile he wrote of Andy Aldrich who became its director. Out of this project, now discontinued, came the presently functioning Aldrich Nursery School, the library of which was started as a Memorial to Helmholz.

He was determined to avoid in the Pediatric Section the impersonal attitude which bigness of organization almost inevitably brings. It was George Logan who finally convinced him that the Fellows did not really want to make rounds on Sunday. His own responsibility to pediatric teaching would not have permitted the thought of this relaxation.

Through all the variety of his Clinic experience, his patients never failed to sense his personal concern. In his years of private practice he had learned the importance of the doctor-patient relationship at the bedside and in the dispensary. Roger Kennedy tells the story of the child who after being examined by Helmholz said, "But I came to see Dr. Mayo," and immediately Charlie Mayo was summoned.

The overriding importance Helmholz gave to a close relationship between physician and child comes to mind in reading the tribute he wrote for the *Festschrift* published by the JOURNAL OF PEDIATRICS on the occasion of Czerny's seventieth birthday. After giving biographic details and describing the great scientific contribution made by Czerny to modern pediatrics, Helmholz adds a note which almost goes unnoticed. It reads, "There is another book which represents Czerny at his best, a little book entitled "Der Arzt als Erzieher des Kindes." The line pays homage to Czerny's achievement and places the book in its proper level of significance. But more than this, one detects the unspoken thought, "This is the book I wish that I had written."

Helmholz's visits to Milwaukee usually came as stopovers to and from one of the many committee meetings he attended or during the Christmas holiday. During these brief interludes, his love-bestowing family gracefully and gratefully accepted his off-the-cuff consultation remarks, such as, "Better to have a thousand dollar orthodontia bill than a five thousand dollar psychiatry bill," or "The pediatrician is in a better position to determine the need for tonsil removal than the laryngologist." The family was less inclined to regard his politically liberal affirmations as equally authoritative.

His enormous energy, like steam under pressure, kept him physically and mentally in the midst of things. He had played tennis back of the anatomy building at Baltimore and had found Rollin Woodyat an able opponent in Chicago. When he moved to Rochester, he lost no time in organizing the Rochester Tennis Club where he continued to play and even helped teach the game to his grandchildren. It was a particular pleasure of his later years to see tennis and the Rochester Tennis Club, which he had done so much to foster, flourishing and providing

opportunities for exercise and healthy competition to so many of Rochester's residents.

It was partly this restless energy which made him so successful a participant in the larger areas of public health. For this, he had superb qualifications, unflagging energy, professional competence, a great capacity for getting along with people of differing points of view, and unswerving integrity. "He was the best man I ever knew to have on a committee," wrote one of his colleagues. "No one would ever think of questioning his motives or his devotion to ideals," wrote another.

Director of the Chicago Infant Welfare Society, Chief of Staff at the Children's Memorial, Chairman of the Section of Pediatrics of the American Medical Association, Editor of the *American Journal of Diseases of Children*, President of the American Pediatric Society, President of the American Academy of Pediatrics, Executive Committeeman of the 1940 White House Conference, and Chief Pediatric Consultant for the 1950 Conference were only some of the positions he so ably held. On all of these he left the imprint of his active mind. Small wonder that one of his Hopkins' classmates, eulogizing him in a letter, said, "I know this sounds a bit as though he might be bearing a banner marked 'Excelsior,' but it was simply that he felt that a man ought to give the best there is in him. He did just that."

In 1943 the honorary degree of Doctor of Science was awarded him by the University of Wisconsin.

It was during the Seventh International Pediatric Congress at Havana in October, 1953, that Helmholz's ease in collecting encomiums struck its first snag. As Fanconi tells the story.

"The congress committee had spread the news over the broadcast that amongst others Professor Helmholz and myself were to be awarded this title by the University of Havana. The event was also mentioned in the printed program and the ceremony ought have taken place on a Wednesday evening. In the morning of the day we both found a little hand-written note in our hotel rooms saying that the Faculty of Medicine of the University of Havana had unanimously nominated us doctores honoris causa, but that unfortunately the ceremony had to be postponed for certain reasons which were not explained. Later on we learnt that they were of political nature. Professor Helmholz felt at first rather vexed, for he had taken along with him the voluminous and heavy academic robes and huge hat and had had much trouble to find a place for them in his small trunk. But soon afterwards we began to laugh heartily about this episode and have done so many a time later on. Now 6 years have passed since the congress in Havana, but the award of the promised academic title is still being postponed!"

In the half century from 1908, the year of his first child welfare appointment in Berlin, to 1958, when he sent in his final report as Medical Director of the Parent-Teachers Association of America, Henry Helmholz had served in some capacity with every movement which concerned the child. He had achieved every honor American pediatrics and its related fields could offer.

Helmholz was one of the group of 20 or 25 men who, led by Clifford Grulee, helped organize the American Academy of Pediatrics. One of the Academy's unique accomplishments, aside from its professional program for its members, was the prodigious job done in cementing the relations between the physicians of the American Continents, the United States, Mexico, and Central and South America. This harmonious relationship, free of diplomatic protocol, had its inception in 1939 when Henry Helmholz in his presidential address advocated the formation of the Committee on Central and South American Scholarships. He served as the chairman of a committee which lined up the pediatric teaching clinics and arranged for scholarships to be given to promising Latin American students. Later, at the Children's Pan American Congress in Washington, Helmholz and Schlutz were in charge of hospitality for Latin American physicians. At this, and subsequent meetings, wrote Dr. Gomez of the Hospital Infantil de Mexico, "The Helmholzes won for themselves and for their country our deep regards," and,

added Dr. Gomez with courtliness, "Mrs. Helmholz was the best social ambassadress ever known to tighten the bonds of friendship, understanding and love between foreign countries and the U.S.A."

The planners of the Fifth International Congress had their misgivings about it. Dr. and Mrs. Emmett Holt in attending to all the details of the meeting did a superb job, but no one was unmindful of the fact that only two years had elapsed since World War II. On the humid July morning the Congress convened, the world, as seen through the *New York Times* of that day, was "filled with distrust and threats."

Two thousand physicians came to New York from 60 countries. When the Congress was over, Borden Veeder was moved to voice the general feeling in an editorial, saying, "The holding of the Congress shows that there is still a background of peace and decency left in the world." According to many who attended it, a good deal of the success of that Congress belonged to Henry Helmholz. As president of the Congress, he gave the opening address which established the tone of the meeting. He contrasted the constructive efforts of the individual physician in saving the life of a single child with the wholesale destructiveness perpetrated through violence. He called on the pediatrician to be mindful of his responsibility in the training of the child's character if we are to have a world where the golden rule remains the measure of humane attitudes. Wallgren called the talk "a masterful event in every way," adding that "all those who had the pleasure of attending the Congress certainly never forgot the achievement of Henry Helmholz and his collaborators." "The deep humanity of the opening address was quite outstanding," writes Fanconi, who related an incident which, while not part of the official proceedings, lifts them to a height the prepared speeches could not attain. After the opening session of the meeting, Fanconi recalls, "Helmholz came up to me and said, 'You are Swiss and know German and French. Please tell the 3 Russian colleagues who attend the Congress that certain remarks in the opening speeches were not meant to be as rude as they might have sounded.' " A letter from one of Helmholz's Hopkins' classmates comes to mind. He writes, "Perhaps the simplest way to summarize his character and personality would be to give the estimate that was universal among his classmates. They knew him as a man who was gifted but free from vanity, whose fineness of character and conduct carried with it no hint of self-conscious superiority or righteousness, and whose essential loyalty to the best could infallibly be depended upon."

At the Sixth International Pediatric Congress in Zurich, Helmholz presented a plan for the permanent organization of the International Pediatric Congress. Mindful of the plan he had presented at the preceding Congress, he urged a broadening of responsibility for the pediatrician to include, in addition to physical health, the mental, emotional, and social development of the child. Forty years had passed since, with Hamill, Ingen, Veeder, and others, he attended the first meeting of the American Association for the Study and Prevention of Infant Mortality, where he had read a paper on the dangers of milk sugar in the feeding of infants. The small clinical world of 1910 had considerably extended its boundaries.

Early in his career Helmholz was impressed with the relations of social problems and child health. For him, pediatrics had lost its sense of a private domain when, in his 1915 study of the mortality rate among the 10,000 who attended Chicago's infant welfare stations, he found that 93 per cent of the deaths occurred in families whose weekly income was $15.00 or less. He had attended the First White House Conference on Child Health called by Theodore Roosevelt to consider the desirability of establishing a bureau within the federal government which would concern itself with all matters pertaining to children. He had participated in every succeeding White House Conference; he was a member of the Executive Committee of the 1940 Conference, of the President's Planning Committee, and Chief Pediatric Consultant

to the Staff for the 1950 Conference.

Through his collaboration with successive White House Conferences, Helmholz lost the traditional medical distrust of governmental social planning. Many of his politically conservative colleagues could not still their anxiety that any federal intercession into medical practice would ultimately lead to the extremes of federally controlled medicine. The diverging viewpoints came to a clash in the now forgotten Children's Bureau-Academy incident. While the Children's Bureau had played a pivotal part in carrying out the Emergency Maternity and Infant Care (EMIC) program enacted by Congress to provide medical services for the mothers and children of men in the Service, the Academy of Pediatrics had given its full cooperation to the program. When the war ended, the directorate of the Academy found reasons to believe that the Children's Bureau planned to continue the EMIC program, hoping thereby to introduce a form of socialized medicine. In the controversy which ensued between the Children's Bureau and the Academy of Pediatrics, Helmholz appeared as a protagonist of the Children's Bureau, which disavowed the intention imputed to it by the Academy. A nine-man committee representing the Children's Bureau, the Academy of Pediatrics, and the American Pediatric Society healed the impending breach between the Academy and the Children's Bureau. Through the joint study of pediatric services, which came out of the controversy and which was suggested by Helmholz, the two contending organizations again worked harmoniously together.

A footnote to this spirited controversy illustrates, more than do the official records, the delicate decency of Hemholz's idea of friendship: In 1944 the controversy was at its height. Dr. Martha Eliot of the Children's Bureau was asked by the Academy officers to answer publicly twenty questions about the Children's Bureau and certain congressional bills which had to do with governmental medicine. When Dr. Eliot, troubled by the attitude reflected in the questions and disheartened by the experience, left the meeting she found Dr. Helmholz sitting outside the door waiting for her. He posed no questions and offered no consoling word but asked her if she would go to dinner with him.

In 1947 Helmholz was named Chief Medical Consultant for the United Nations International Children's Emergency Fund (UNICEF). This gave him the opportunity to be associated with the largest mass immunization program ever carried out. Fifteen million children and adolescents were vaccinated with B.C.G. He saw the UNICEF mission as an opportunity to bridge the division between the "haves" and "have nots" of Europe. Swiss and Scandinavian physicians carried out the program. During the year, Dr. Helmholz visited Austria, Hungary, Poland, Czechoslovakia, Italy, and other countries.

Letters to the family written by the Helmholzes during their experiences with UNICEF reflect their broad interest in medical problems and give an occasional glimpse of human adventure.

From Warsaw: "The first shops to appear in the main street of Warsaw were florists' shops, because the greenhouses being out in the country were not destroyed and so the owners had something to sell. . . . The Polish Red Cross is building a preventorium of 600 beds. . . . The thing that struck us through the trip was the amount of help that Switzerland and Sweden were contributing to the rebuilding."

From Hungary: "Visited Dr. Kun of the Welfare Section on protection of children. He stated that the abandoned children had been reduced from 45,000 to 25,000."

From Greece: "Dr. Choremis, the Professor of Pediatrics, has treated some 80 cases of tuberculous meningitis, which before the advent of streptomycin was always fatal. With streptomycin only 25 per cent die. His budget for teaching is about $200.00 a year. . . . Except for a trip to Corinth where we saw the rostrum from which Paul addressed the Corinthians, I did little sight seeing."

The last top official position held by Helmholz was that of Medical Director of the

National Parent-Teachers' Association. As with all his assignments, he had to be a pioneer. Fluoridation for the prevention of dental caries became his new enthusiasm. Before the American Public Health Association, in published articles, and in a paper before the first plenary meeting of the Copenhagen Congress, he presented the advantages of fluoridation to the community. His report to the P.T.A. on the completed job was his final official act.

The enthusiasms of Henry Helmholz in the whole range of pediatrics were, in a way, the counterpart of his bodily temperament. As he gave his physical energy to tennis or track, just so he put his brain and heart into pediatrics. It is this personal investment rather than his 200 contributions to medical literature which those who knew him recall. In his concern for the child, he was prepared for the bold leap in the field of public health which many of his "practical" minded colleagues avoided. He had come to understand that social forces had as much to do with what happened to children's welfare as do doctors' prescriptions.

His laboratory investigations revealed no such complex elements. They were examples of orderly planning and exact reporting. The extravagant phrase is missing from his reports as was the intemperate word from his speech.

On rare occasions, the exactness of his sense of propriety and fair play gave a temporary impression of arbitrary formality, as when, in his capacity as chairman of one of the sessions of the Fifth International Pediatric Congress in 1947, he denied Professor Preben Plum, Head of the Pediatrics Department at the University of Copenhagen, more than his alotted time. Helmholz had often witnessed the unfair exclusion of some person's talk because previous speakers had used up the time. Rules therefore had to exist, not for conformity or for discipline's sake, but in order that in exercising our rights we should not infringe on those of others. "I was just getting to the conclusion," writes Dr. Plum, "when Dr. Helmholz, in his capacity of chairman, stopped me. I told him I had not used my time up and asked him to have 30 seconds to tell my conclusion, but he was not to be persuaded. In the following argument with Dr. Helmholz, whom I had not met before, I am afraid I was very emotional about the happening, and told him that I did not think highly of his abilities as a chairman. This was the beginning of a lasting friendship between us during which my feelings for Dr. Helmholz changed into deep affection and great admiration. I had the great pleasure to stay in the home of Dr. and Mrs. Helmholz in 1950, enjoying their great hospitality and the humanistic and cultural atmosphere of their family life."

The guest book of the Helmholzes was a Who's Who in contemporary pediatrics. Its international character illustrated Henry's conviction of the importance of a peaceful world and the relatedness of men.

On Aug. 19, 1958, a Western Union message came announcing the death of Henry Helmholz. Services were held in the Universalist Church. Afterward, intimate friends gathered at the Helmholz home to share a few moments with Isabel and the immediate family, the sons, Dr. Lindsay Helmholz, professor of chemistry at Washington University, St. Louis; Dr. Frederick Helmholz, Jr., a member of the Section of Physiology of the Mayo Clinic; Dr. Carl Helmholz, professor of physics at the University of California, Berkeley; and the daughter, Margaret, now Mrs. Howard Burchell of Rochester.

We sat about and spoke our second thoughts, leaving our first for a later time. I had not seen Isabel and Henry's children for some years, not since their college days. Each reminded me in some way of Henry, the same modesty, the same reserve, the same friendliness. A curious sensation that these voices, these cadences, and rhythms were his and not theirs came over me. I thought of how much like their father they all were, and of Rilke's poem:

"And so we stand with mirrors: someone here,
and someone there, with no agreement reached;

but catching, though, and passing the reflection we've singled out from far, this pure reflection, on to another from the gleaming mirror"—

which was Henry Helmholz.

ABRAHAM B. SCHWARTZ

The writer gratefully acknowledges the help of these people who, in person or by letter, supplied information used in this Profile: Drs. Sam Amberg, Roger Kennedy, George Logan, and Hadow Keith, Section of Pediatrics at the Mayo Clinic; Professor Fanconi, Zurich; Professor Wallgren, Stockholm; Professor Plum, Copenhagen; Professor Frederic Gomez, Mexico City; Drs. Damon Pfeiffer, Frank Hinman, and Harvey Stone, intimate classmates of Helmholz's days at Johns Hopkins; Drs. Borden S. Veeder, Richard M. Smith, Allan M. Butler, Edwards A. Park, Martha M. Eliot, Warren R. Sisson, Louis Sauer, J. B. Bilderback, and Angus Cameron; Mrs. Robert Leonard, Helmholz's Secretary at the Mayo Clinic, and Carol Beeler de Takats, his bacteriology assistant at the Children's Memorial Hospital. Especially, he thanks Isabel Helmholz and members of the Lindsay and Helmholz families.

Correspondence

To the Editor:

1. Are there misprints in the case reports on page 495 of the JOURNAL for October or did Dr. Call fail to discuss some noteworthy facts in his patients' lives? Case 1, Mrs. T., is described as 32 years old and "married for 11 years"; her husband is "a 26-year-old major." There is no indication that this rather youthful major is her second husband, so one must conclude that at the age of 21 Mrs. T. married a 15-year-old boy. Surely this, if true, is worthy of some comment.

Nor is there any discussion of the fact that Mrs. T. had adopted a child 5 years previously. Unless the adoption was primarily for the sake of the child (e.g., a war orphan), this would seem to indicate a problem of infertility. Isn't it possible that infertility and difficulty with lactation are related and that there might be some physiologic cause, such as a hormonal deficiency?

Case 2, Mrs. L., according to the figures given, was married at 15 to a 19-year-old boy. Mrs. L. is described as "primitive," which at first glance seems to be an understatement. It would be interesting to know if marriage at 15 is usual in Mrs. L.'s socioeconomic class.

2. While on the subject of Dr. Call's article may I enter an objection to one of my special dislikes: "a general survey type study" (beginning of Summary, p. 493). Why the all too ubiquitous "type"? A general survey, or a study, or a general-survey study, but please leave out the "type" or, if you must use it, say "type of study."

3. Another figure which surprised me in the October JOURNAL was the white blood cell count of the patient discussed in the Clinical Pathological Conference. On page 522 it is given as 161,000. Is that to be expected in acute infectious polyneuritis? It isn't mentioned in the seventh edition of your text. None of the participants in the Conference mentioned it, so I wondered if your decimal point had slipped.

4. Dr. Veeder's experience with the Cystic Fibrosis Foundation has stimulated me to take up again an idea I have thought about for some time. I should like to start a Foundation for Research in Prolonging Life. All the grants from this Foundation will go to physicians in private practice who will spend the money on recreation. The Foundation will publish illustrated brochures, produce television shows, etc., dramatizing their latest figures on the relative efficiency, as life-prolongers, of camping versus resort hotels, one long versus several short vacations, theater versus golf, Europe versus South America, and so forth. Campaign literature will prove that 7 out of every 10 will die because they relax the wrong way, and nothing can save them but more *basic* knowledge about recreation. Perhaps the JOURNAL would like to have the honor of announcing the initial fund-raising drive.

M. EUGENIA GEIB, M.D.
MADISON, N. J.

1. *To the Editor:*

In reply to the letter sent by Dr. Geib I would like to say the following:

Yes, this was the second marriage for Mrs. T. The adoption came about because Mrs. T. had not been able to become pregnant and, as is so frequently the case, Mrs. T. was able to become pregnant following the adoption. The relationship between various hormones and their effect upon milk production and milk ejection is acknowledged fully and discussed in the body of the paper. In Mrs. T.'s case it was evident that no problem in milk production was present since she developed excessive engorgement and caked breasts. The problem was one having to do with the release of milk from the breasts which, as has been noted, depends upon the integrity of the milk ejection reflex which I have alluded to in the paper but did not describe fully since there are adequate descriptions elsewhere, as, for example, in the papers by Newton. The smooth operation of the milk ejection reflex in human beings, cows, and pigs has been shown to be related directly to psychological factors. There is no need to postulate a hormonal deficiency in Mrs. T. since actually she was able to become pregnant and there was no clinical evidence of any hormonal deficiency.

Much as I might have wished to, I did not perform psychiatric examinations on the 100 women studied, but my observations were made within the setting of pediatric care.

JUSTIN D. CALL, M.D.
UCLA SCHOOL OF MEDICINE

2. No argument—"no type."

3. White blood count should have been 16,100 per cubic millimeter. An erratum was inserted in the March, 1960, issue.

4. With enthusiasm we join tongue-in-cheek Eugenia in her proposal for a new "Foundation" —provided, of course, that preferential rating for the testing of vacation spots is accorded aging and weary Editors.

Re the Jenner Statue

To the Editor:

A number of letters have been received since the story of the removal of the Jenner statue in the August issue of the JOURNAL which throw a little more light on the affair. Some consider the removal from Trafalgar Square as a "disgrace," while others look upon the site in Kensington Gardens as preferable. Ignorance of the statue is not confined to the pediatricians. Mr. William LeFanu, Librarian to the Royal College of Surgeons in Lincoln's Inn Fields, wrote, "I am not surprised to hear that you found that so few people knew about this statue. I remember ten years ago at the time of the centenary our President Lord Webb-Johnson asking members of the Library Committee if they knew where the statue of Jenner stood, and not one of a half a dozen leading surgeons could answer him: he and I were both much amused."

Mr. Payne, Librarian of the Royal College of Physicians, again furnished help. Interested in the speculation as to whether or not the Ministry of Works might contain the answer as to why the statue was removed, he got in touch with the Librarian of the Ministry of Works and kindly sent me a copy of the following letter he received in reply. Permission for publication was courteously given by the Ministry of Works.

MINISTRY OF WORKS
LAMBETH BRIDGE HOUSE,
LONDON, S.E.1

Dear Mr. Payne:

Your letter of 15th October to our Chief Librarian has been passed to this Section for reply.

Our First Commissioner applied to the Treasury in 1861 to have the statue of Jenner moved as its differing scale and sitting position were at variance with the existing statuary in the Square. The statue was re-erected by Mr. J. Thomas in February, 1862, in Kensington Gardens with the approval of the Jenner Committee and by Her Majesty's gracious permission.

The move must have caused some controversy as the following lines appeared in Punch at that time:

> "I saved you many million spots
> and how you grudge one spot to me."

I regret our inability to be more informative.

Yours sincerely,

Signed: MINISTRY OF WORKS

We leave it to the reader to draw his own conclusions as to the real reason.

Another correspondent raises a point that is quite intriguing. According to history many military campaigns and wars throughout the ages have been won or, better stated, perhaps lost as the result of pestilence and disease rather than the use of arms. Is not Jenner therefore entitled to be considered a military hero worthy of a statue in Trafalgar Square? It brought back to my mind the military consternation and uproar that developed when several cases of smallpox developed among the troops at a British Military Base in France where I was attached in the spring of 1918—just at the time when the Germans nearly split the Allied line. Due to Jenner's discovery the situation was soon under control.

Another raised the question of whether there is not a statue of Florence Nightingale in the Square. This raised an amusing "slant" until it was found that the statue erected in 1915 stands in Waterloo Place at the south end of Regent Street.

A British pediatric friend called my attention to an error in the story. It is not so much the litter of the pigeons that dirties the Square as it is that of the starlings. So with an apology to the *Columbidae* the story ends. If it is ever our good fortune to visit London again, "Kensington Gardens, in the vicinity of the stone bridge spanning the Serpentine, on the Bayswater side" has a high priority.

BORDEN S. VEEDER.

To the Editor:

I wonder if there is some way of alerting pediatricians and virologists to the following circumstances to see if similar incidents have been observed elsewhere.

In the November, 1959, issue of *Neurology* under the title "Acute Cerebellar Ataxia in Children" is the following sentence: "Two patients, both of group I, received their second injections of Salk vaccine one and three days prior to the onset of the ataxia. . . . Also, two children (one from each group) had received two and three injections respectively of Salk vaccine several months prior to onset of illness. In view of previous assertions of a possible relationship between acute cerebellar ataxia and unusual manifestations of poliomyelitis, future reports of all cases of ataxic children who have had the complete series of Salk inoculations will be valuable in determining if such an association exists."

On April 7, 1959, I saw a child 3½ years of age with a history of acute onset of ataxia. She was picked up at the nursery school unable to stand because of dizziness and staggering. It lasted for several hours; she then improved but in a few days had a recurrence. There was no history of previous illness. She had been seen elsewhere for this illness and no cause was established. She had a history of immunization with DPT and poliomyelitis vaccine and it was recorded her next polio vaccine was due in the summer. The relationship of the last one to the ataxia was not determined. On Nov. 6, 1959, she reported again and then stated that in July she had a third Salk vaccine injection followed by a similar staggering episode. The mother then reported that her first ataxic symptoms followed her second Salk vaccine. I examined this child after the first episode and found her still somewhat ataxic.

H. E. THELANDER, UNITED CEREBRAL PALSY ASSOCIATION OF SAN FRANCISCO PRE-NURSERY PROGRAM OF CHILDREN'S HOSPITAL

Books

Pediatric Neurosurgery.

Ira Jackson, M.D., and Raymond K. Thompson, M.D., Springfield, Ill., 1959, Charles C Thomas, 564 pages. Price $16.50.

This book is the work of 24 neurosurgeons and specialists in the allied fields of pediatrics, neurology, anesthesiology, and plastic surgery from various general hospitals, private clinics, and university hospitals throughout the United States. The opinions expressed in this volume represent the current concept of the management of the neurosurgically ill pediatric patient throughout a cross section of the country in medical facilities other than pediatric neurosurgical centers.

The editors have emphasized that pediatric neurosurgery is not adult neurosurgery in miniature but that it must be considered as an entirely separate entity amounting almost to a subspecialty of neurosurgery. The small size of the patients, coupled with the anatomic and physiologic differences from adults, requires not only close cooperation between the neurosurgeon and allied specialists but also specifically designed diagnostic facilities, operating rooms, instrumentation, and operative techniques.

The book is divided into two parts. The first section is concerned with diagnosis and management. The chapters on pre- and postoperative care and on organic neurology are well done and should be valuable for the pediatrician. The chapter on diagnostic techniques is severely lacking in detail. The authors describe the basic diagnostic techniques only as they differ from their performance in the adult. They draw heavily upon the reader's own knowledge of the performance of these tests in general and fail to mention more recent refinements of technique. This chapter is of possible value only to the neurosurgeon and should not be used as reference for the performance of any of these tests by anyone who is not a trained operator.

Part II consists of 14 chapters written by neurosurgeons and covers in well-organized detail the surgical disorders of the nervous system in infants and children. So much information collected in one volume makes it a valuable reference text for all physicians handling pediatric patients.

The chapter on hydrocephalus is of special interest. The subject is treated rather lightly for a work of this magnitude, and no new solution to this perplexing problem is offered. The authors present, however, a clear picture of the present status of the management of hydrocephalus with the numerous shunt mechanisms which have been devised. They point out that there is "nothing new under the sun" in this respect and that there is no shunt procedure currently available which has been proved to function consistently in all types of hydrocephalus. The more recently developed modifications of the shunt and the valves used, which seem to hold some promise of sucess, are described. The authors caution, however, that these procedures must stand the test of time before their true value can be evaluated fully.

FREDERICK MURTAGH, M.D., F.A.C.S.

The Surgeon and the Child.

Willis J. Potts, M.D., Philadelphia, 1959, W. B. Saunders Company, 255 pages. Price $7.50.

The title of this book is well chosen. It is not professed to be another complete text on pediatric surgery. Rather it reflects clearly and intimately the practical and often humbling experiences of one of the world's most prominent pediatric surgeons. Willis Potts has contributed many well-known major technical advances to the field of pediatric surgery. Equally important and stimulating to those who know him or are familiar with some of his less technical articles is his continued expression of practical and humane philosophy and inquiry into the surgical care of children.

The first few chapters deal with the general aspect of the highly specialized field of pediatric surgery. They are presented in a manner and with a philosophic accompaniment which will be enjoyable and profitable to all who are charged with the care of sick children.

Succeeding chapters record the methods of diagnosing and treating specific surgical conditions in infancy and childhood. Each is discussed in practical general terms and accounts of failures are more often used to illustrate points than the more common successes. Always the care of the total individual child and his parents before, during, and after operation is given first consideration.

There are many dogmatic statements with which others skilled in the field will argue. These are excused in the postscript as being purposefully made to "sharpen the focus upon diagnosis and treatment."

This book will be enjoyed and profitably read by all who are interested in giving the "deformed or surgically ill infant and child the best care available."

GEORGE P. PILLING, IV, M.D.

Laboratory Manual of Pediatric Micro-Biochemical Techniques.

Donough O'Brien and Frank Ibbott. Denver, 1959, University of Colorado Medical Center Press. Distributed by J. W. Stacey, Inc., 2575 Hanover St., Palo Alto, California, 164 pages. Price $3.50.

In their foreword the authors cite the growing demand for micromethods in hospitals and institutions other than those primarily for infants and children. This sturdy, paper-bound manual is a welcome addition to the rather limited number of books specifically designed to meet this demand. It briefly describes the microchemical techniques currently employed in the authors' own laboratory. It seems evident that the final choice for each technique was made only from a wide knowledge of the literature. In a few instances the original source for the modification of the technique presented is not given. The index lists over 100 procedures, a number of which frequently are not performed in general hospital laboratories, but which might be added to their routine, with the ensuing gratitude of pediatricians. The aliquots of sample used are 0.1 ml. or more, the opinion of the authors being that ultramicro procedures are not practical for clinical laboratories. A table of normal values is included.

A more detailed description of the apparatus and general techniques particular to microchemistry would have made the manual more useful to those workers who have no previous acquaintance with microprocedures. However, it does demonstrate to the relatively uninitiated what the possibilities are for microchemistry in a routine clinical laboratory. Perhaps this manual may prove to be more stimulating to laboratory staffs which specialize in pediatric chemistry, but which have yet to provide as comprehensive service as is apparently available to the clinicians in the Department of Pediatrics of the University of Colorado Medical Center.

MARY L. BAUMANN

Infectious Diseases of Children. Saul Krugman, M.D., and Robert Ward, M.D., St. Louis, 1958, The C. V. Mosby Company, 340 pp. Price $10.00.

This book succinctly presents the clinical patterns of the common as well as of many of the rarer infectious diseases which are likely to occur in infants and children in this country. The practical aspects of diagnosis and management are clearly presented. The chapter on the differential diagnosis of the acute exanthematous diseases is especially good. There are many excellent charts, sketches, and photographs showing characteristic clinical courses, rashes, and the like.

The authors are to be commended for the preparation of this practical book on infectious diseases which will be useful to both student and practitioner and as a handy reference volume for hospital interns and residents.

ROBERT H. HIGH, M.D.

Pediatric Pathology.

Daniel Stowens. Baltimore, 1959, The Williams & Wilkins Company, 677 pages. Price $20.00.

Perhaps a pediatrician is not qualified to review an opus on pediatric pathology especially since the preface states that this book "was written with the hope that it would be of assistance to the pathologist." Such a text, however, certainly should be welcome to all physicians interested in any aspect of pediatrics. I am in complete accord with the author that there is a great need for such a book since pediatric pathology has indeed come of age as a recognized subspeciality.

The organization of the book follows that of other texts on pathology. The first 19 chapters discuss pathologic conditions from an etiologic point of view. Thus there are chapters on diseases caused by bacteria, spirochetes, poisons, nutritional disorders, hypersensitivity, and so on. Chapters 20 to 35 deal with the pathology of the systems of organs. There is an appendix which is an analysis of the first 10,000 cases entered in the files of the American Registry of Pediatric Pathology, and it is this wealth of pathologic material that largely forms the basis of this book. A brief clinical description introduces each disorder and this is followed by a discussion of the pathologic changes. Gross descriptions are minimal, with the emphasis being placed on the microscopic appearance of lesions. In keeping with the author's de-emphasis of the gross description of pathologic changes, there are virtually no photographs of gross specimens. In my opinion this detracts considerably, especially in certain sections such as that on diseases of the heart. The book, however, is illustrated profusely with photomicrographs which are uniformly of superior quality. The format of the book is attractive, pleasing to the eye, and easy to read.

The principal shortcomings of the book are twofold. First, there is a lack of depth in pathologic description. The clinical introductions often are longer than the pathologic descriptions and unfortunately contain some errors. For example, children with progeria are incorrectly said to be "most often defective mentally," cystinosis is said to be characterized by "hyperphosphatemia" (probably a typographical error), and mental retardation is said to constitute part of the Mauriac syndrome whereas hepatomegaly is not even mentioned. In a description of ovarian agenesis, it is stated that "malformations of the genitalia are always present and include atrophy or hypoplasia of the clitoris, rudimentary uterus, hypoplasia of the fallopian tubes. . . ." This may be true for the untreated adult with the disorder, but certainly it is not an accurate description of an affected child and is misleading in a text on pediatric pathology. Certain sections of the book are quite complete whereas others are superficial and cursory. Thus one is distressed to find 1½ pages devoted to plague and only a short paragraph on galactosemia. Syphilis, a subject adequately covered in all texts on pathology, is given 12 pages, but pediatric entities such as listeriosis and oxalosis are dismissed in a few sentences in the differential diagnosis of herpes simplex infection and renal rickets, respectively. Phenylketonuria is passed off with the statement, ". . . no anatomic disturbances of diagnostic significance have been described in this disease." Perhaps the marked lack of myelinization that has been reported in the literature is not "diagnostic" but it is worthy of inclusion in a text on pediatric pathology.

The second shortcoming stems from the fact that "the book is replete with hypotheses, new terms, altered classifications. . . ." The author continues in the preface, ". . . if these ideas arouse howls of disagreement or scorn, they still serve the purpose of showing the existence of problems which, up to the present, did not seem to exist." Others, I'm sure, will disagree with some of the speculations in this book and I would like to register one "howl" concerning Dr. Stowens' deliberations on the pathogenesis of "mixed adrenal disease of infancy" (salt losing form of congenital virilizing adrenal hyperplasia). The statement is made that "it seems probable that the change in the adrenal . . . may be the result of functional as well as anatomic malformation and hypoplasia of the kidneys, in an attempt to compensate for the latter." Such a hypothesis is contrary to all the known facts and is most misleading to the reader unfamiliar with the subject.

In spite of these criticisms, the work on the whole fulfills its declared intentions of demonstrating that pediatric pathology is a separate discipline. The well-informed pediatrician, however, is likely to be disappointed in the use of the book as a reference.

ANGELO M. DI GEORGE, M.D.

Tumors of the Pancreas.

Virginia Kneeland Frantz, Washington, D. C., 1959, Armed Forces Institute of Pathology, 149 pages. Price $1.50.

This publication is designed primarily for pathologists and is one of a series of fascicles published by the Armed Forces Institute of Pathology as an atlas of tumor pathology. The voluminous illustrations are of superb quality and the text is clean and concise. As is to be expected, the material deals principally with

neoplasms of the pancreas as encountered in adults, but there is more than casual reference to neoplasms of the pancreas in infants and children. For example, Table 1 lists all of the carcinomas of the pancreas which had been reported in the literature at the time of publication. Although the fascicle is hardly one which would interest most pediatricians, it should serve as a valuable reference to anyone specifically interested in tumors of the pancreas in any period of life.

JAMES B. AREY, M.D.

The Birth of Normal Babies.

Lyon P. Strean, Ph.D., D.D.S., F.A.P.H.A., New York, 1958, Twayne Publishers, Inc., 194 pages. Price $3.95.

It has been possible for two decades now to alter experimentally the development of mammalian embryos in utero by external environmental factors. A recent review showed that over 50 methods are available to induce congenital malformations in mammals by environmental teratogenic agents. At the same time it has become known that exposure of human embryos or fetuses to therapeutic or atomic radiation, to the German measles virus, to *Toxoplasma gondii,* to Aminopterin, to goitrogenic factors, or to certain progestins can result in congenital malformations. Although there is a possibility that many other environmental factors are teratogenic, proof for this is lacking. At the present time the percentage of congenital malformations occurring in man and known to be due to environmental factors acting during pregnancy is still very small. In spite of this lack of information, exaggerated statements have been made in the medical and lay press asserting that most congenital malformations can now be explained by adverse events occurring during the first trimester of pregnancy. The book under discussion represents probably the most extreme literary product of this type.

The case of Alice serves as the "eye opener." While Alice was pregnant, she learned that her husband had two children by a previous marriage and quarreling ensued. In the midst of a violent quarrel the husband kicked Alice in the stomach. In due time a handsome little boy was born who had only one of the long bones of his right forearm. The author said, "Alice, your case history has suggested the possibility that most congenital abnormalities are not hereditary but due to stress." Since under stress the anterior pituitary gland produces an increased quantity of ACTH which stimulates the adrenal cortex to produce an increased quantity of cortisone, the author asks, "Did the abundance of cortisone manufactured by Alice's adrenal cortices produce an abnormal intrauterine environment which interfered with the development of those rudimentary cells which were destined to produce a long bone in the right arm of the offspring?"

To test the hypothesis the author, in a retrospective study, obtained information by questionnaires from 228 mothers of children with harelip and cleft palate. The results suggested to the author that the factor common to all of these mothers was traumatic, physiologic, or severe emotional stress occurring around the sixtieth day of pregnancy when the right and left maxillae fuse. Only a few examples of the type of proof offered can be cited here. There were only 7 Negro mothers whose children had cleft palates in comparison with 221 children of white mothers. The author states, "One may explain the low incidence of cleft palate in Negro children, in this study, on the basis of higher frustration tolerance in the Negro population as compared to white pregnant women." This will be confusing to the student of psychosomatic medicine who is told by other authorities that the high incidence of essential hypertension and hypertensive cardiovascular disease in Negroes is due to severe emotional stress conditioned by the social milieu of the patients. Thus, the higher frustration tolerance of Negroes apparently is not accepted generally in psychosomatic medicine.

The inquiry also showed that there was, in the author's sample of patients with cleft palate, a higher incidence among firstborn children than among secondborn children and a higher incidence among secondborn children than thirdborn children, etc. This high number of firstborn children among cleft palate patients is turned imperceptibly by the author into a high incidence of cleft palate in firstborn children, which is, of course, a very different matter. The result is the following interpretation: "The high incidence of cleft palate in the firstborn may be attributed to the severe anxiety frequently associated with the first pregnancy,

coupled with other stressful situations." Actually, there is no higher incidence of cleft palate among the first than among the second or third children, as shown by MacMahon and McKeown (1953) who found the incidence of facial clefts unrelated to birth rank. The high number of firstborn children among the cleft palate patients can be better explained by the fact that the world, and probably the sample of the author, contain more first than second children and more second than third children. There is no need to attribute this phenomenon to stress. In one case a sixteenth child born to a woman 48 years old had cleft palate, and the author states, ". . . it would not be surprising to find this woman in a state of frustration" thus explaining the origin of this case. In this way stress can explain cleft palate in both the first and the sixteenth child.

The author states that stress causes not only cleft palate but also many other malformations. In fact, he goes so far as to say that "emotional disturbances constitute one of the most frequent causes of congenital malformations" (p. 140). He also asserts that "pregnancy, per se, is a stress phenomenon, and pregnant women manufacture in their adrenal glands more than normal amounts of cortisone." Yet, in spite of the stress and cortisone surrounding mother and child, many children are born normal. The author admits that when two pregnant women experience the same stress phenomenon at the same time, one may give birth to a normal baby and the other may have a defective offspring. This difference is explained by the assumption that some women are more capable of adjusting to severe emotional stress than others. In addition, "under prolonged severe emotional stress the adrenal cortex may show symptoms of exhaustion and it cannot be over-stimulated. Under these conditions the child, if born alive, may not have a congenital defect; however, frequently these mothers do not go to term and may have a stillbirth or miscarriage." Since the theory was never tested by cortisone determinations, it is entirely free of contradictions.

It is admitted that some hereditary influences play a role in some cases. The interpretations by the author of the laws of inheritance are so extraordinary that they deserve to be quoted: "Even where it has been established that clubfoot or cleft palate is an hereditary characteristic in a particular family many of the offspring, in fact, most of them, escape the defect. With the first child the chances of development of an abnormality are in the order of five to ten percent. If the second child also develops this abnormality, then chances for the third child to have the same defect are quite low, that is the chances are one in four that the child will be normal. On the other hand, if the first three children are normal, then the chances for the fourth child to have the abnormality are quite high" (p. 70). This is a unique formulation of the laws of chance.

Since "stress" in early gestation is held to be the cause of congenital malformations, precautionary methods during pregnancy are recommended as a guide to "radiant and blessed motherhood." They are formulated in ten commandments which range from orders to avoid traumatic, physiologic, and emotional stress to suggestions such as "surgical operations under general anesthesia should be performed before conceiving or after birth of the offspring." The author believes that "adherence to the Ten Commandments of Genesis . . . should go a long way to help prevent the development of handicapped children." Such statements may sound like glad tidings, but they are in reality very dangerous, since only few congenital malformations are attributable at the present time to known postconceptional, environmental factors. Malformations which are due to specific genetic factors and determined before or at conception will appear in spite of careful protection of the mother during pregnancy. In such cases the belief in "stress" as the main cause of congenital malformations may be harmful and lead the parents to unjustified self-incrimination or to unjust accusations of relatives, physicians, anesthetists, dentists, or innocent bystanders who crossed the path of the pregnant woman during a "critical period" in the development of the child. Most of the case reports of the author represent such *post hoc, ergo proter hoc* reasoning, recording as they do the type of stress and the abnormality of the offspring. These case histories are difficult to evaluate, since at the end of the list (p. 21) the following statement is found: "Any similarity to a person, living or dead, is purely coincidental. Names of individuals and other criteria for identification in the case histories have been changed."

This book can be recommended to students of the fallacies of present-day pseudoscience.

JOSEF WARKANY, M.D.

All About You: An Adopted Child's Memory Book.

Marion A. MacLeod. Norwalk, Conn., 1959, C. R. Gibson & Co., 72 pages. Price $5.00.

This book has been designed specifically for adopted children to serve not only as a record of the important events in the child's life but also as a guide for parents indicating the observations that will be of interest as well as value in subsequent years. It is arranged well and is illustrated and printed beautifully.

A removable booklet entitled "Let's Talk With Adoptive Parents" is included with each book. This contains several short articles by individuals interested in adoption and should be helpful to parents in telling the "adoption story" to their child.

JAMES MARVIN BATY, M.D.

Involution of the Ductus Arteriosus. A. Sciacca and M. Condorelli, Basel and New York, 1960, S. Karger, AG., 52 pages. Price sFR. 7.

This very interesting monograph consists of two parts. The first is a critical review of the literature; there is disagreement with many of the conclusions in the preceding studies. The second part details an original study of the progressive gross, histologic, and physiologic changes occurring in the ductus arteriosus of the guinea pig during the latter stages of pregnancy and the early days of postnatal life. The conclusions are that both anatomic and physiologic closure of the ductus begins considerably before birth and that increasing flow through the pulmonary artery occurs at the same time.

Since these findings differ from those observed in sheep by Born, Dawes, Mott, and Widdicombe (Changes in the Heart and Lungs at Birth, Cold Spring Harbor Symp. Quant. Biol. 19: 93, 1954) and by James and Rowe in human newborn infants (The Pattern of Response of Pulmonary and Systemic Pressures in Newborn and Older Infants to Short Periods of Hypoxia, J. PEDIAT. 51: 5, 1957), it would appear worth while to study ductus of other mammals in a similar detailed way to see what changes occur in relation to birth.

JOSEPH M. GARFUNKEL, M.D.

Diseases of the Nervous System in Infancy, Childhood and Adolescence, ed. 4. Frank R. Ford, M.D., Springfield, Ill., 1960, Charles C Thomas, Publisher, 1548 pages. Price $29.50.

This authoritative text has been revised extensively and rewritten. It is amazingly clear and often disarmingly personal. Dr. Ford's valued judgments are evident on every page. A long, detailed bibliography has been added to this edition and increases its usefulness. Every physician who sees children should have ready access to this text in its present edition.

Although the price of this text seems a bit high at first glance, its contents justify the cost.

HENRY W. BAIRD III, M.D.

News and notes

Harvard Medical School Department of Pediatrics announces two **Spring Courses for Graduates at the Massachusetts General Hospital.**

Pediatrics 3 will be given June 6 to 18, daily from 9:15 A.M. to 4:30 P.M., and will provide a general review with emphasis on recent advances and therapy. The first 7 days will be devoted to pediatric medical, surgical, orthopedic, cardiac, allergic, dermatologic, psychiatric, eye, ear, and x-ray problems. The last 4 days will concentrate on disorders of growth and development, common endocrine problems, and the metabolic aspects of infant feeding, parenteral fluid therapy, and management of nephritic and diabetic patients.

Pediatric Metabolism and Endocrinology will be given June 14 to 18, daily from 9:15 A.M. to 4:30 P.M., and will be the same as the last 4 days of Pediatrics 3, described above, but may be taken separately.

Those interested should write to Courses for Graduates, Harvard Medical School, 25 Shattuck Street, Boston, Mass.

Boston University School of Medicine, Department of Psychiatry, in cooperation with Boston City Hospital, Department of Pediatrics, announces a **training program in the management of emotional problems of children** designed for practicing physicians.

The curriculum includes techniques for the recognition, understanding, and treatment of children with emotional disturbances. Under individual supervision, the trainee will learn how to manage children who, together with their parents, present a variety of emotional problems.

The function, interpretation, and limitations of psychological tests will be presented as well as the techniques of preparation of children for office and hospital diagnostic and surgical procedures. A seminar in the emotional development of children will be available.

The course will be adapted to individual needs in terms of time and intensity of instruction.

For further information write to Box 1, Boston University School of Medicine, 80 East Concord Street, Boston 18, Mass.

The Twelfth Annual Summer Clinics of the Denver Children's Hospital will be held June 15 to 18 in the Granby Recreational Area as a part of Children's Hospital 50th Anniversary Celebration. There will be 4 half-day sessions allowing registrants to enjoy the recreational facilities in the afternoons.

Guest speakers will be Dr. James B. Arey, pathologist, St. Christopher's Hospital for Children, Philadelphia; Dr. John Caffey, radiologist, Babies Hospital, New York City; Dr. H. William Clatworthy, Surgeon in Chief, Children's Hospital, Columbus; and Dr. Harrry H. Gordon, Department of Pediatrics, Sinai Hospital of Baltimore.

For further information write "Pediatric Round Up," Denver Children's Hospital.

The Woods Schools, Langhorne, Pa., announces two **new recordings from its 1958 Spring Conference on "Counseling Parents of Children with Mental Handicaps"** held in cooperation with the University of Minnesota.

The records are "Counseling with Parents at Time of First Knowledge of Retardation," presented by Reynold A. Jensen, M.D., Professor of Psychiatry and Pediatrics, University of Minnesota, and "Helping Parents in a Community Setting," by Harriet E. Blodgett, Ph.D., Program Director, The Sheltering Arms Day School, Minneapolis, and Assistant Professor, Institute of Child Welfare, University of Minnesota.

The school will lend the 35 minute, 33⅓ r.p.m. records, singly or together, without cost except for shipping charges to organizations interested in the problems of parents who have mentally handicapped children.

At the 30th annual meeting of the **American Academy for Cerebral Palsy** in Los Angeles November 30 to December 2, the following **officers** were elected: president, Raymond R. Rembolt, M.D., Iowa City; president-elect, George W. N. Eggers, M.D., Galveston; vice-

president, Herman Josephy, M.D., Chicago; secretary, Joseph D. Russ, M.D., New Orleans; and treasurer, Samuel B. Thompson, Little Rock.

The 1960 annual meeting will be held at the Penn-Sheraton Hotel in Pittsburgh October 5 to 8.

The First European Congress of Pediatric-Psychiatry will be held in Paris at the Nouvelle Faculté de Médecine (New Faculty of Medicine) September 16 to 20.

The biologic basis, stages, and social incidences of maturation will be studied with a closing symposium on psychoanalysis of children.

For further information write to Dr. D. J. Duché, Secrétariat, Pavillon Clérambault, Hôpital de la Salpétrière, 47 boulevard de l'Hôpital, Paris XIII°.

Dr. Charles W. Daeschner, Jr., has been appointed professor of pediatrics and chairman of the pediatrics department of the University of Texas Medical Branch at Galveston beginning July 1. Currently associate professor of pediatrics, at Baylor's College of Medicine, he will succeed Dr. Harry Stoeckle, Jr., acting chairman, and Dr. Arild E. Hansen, who retired from the post last September.

The Cook County Graduate School of Medicine announces a **2-week course in Neuromuscular Diseases of Children** with emphasis on cerebral palsy to be given by Dr. Meyer A. Perlstein June 20 to July 1. Practical clinical aspects of the procedures of treatment and rehabilitation will be stressed.

The fee is $250 and registration is limited. For further information write to John W. Neal, Registrar, Cook County Graduate School of Medicine, 707 South Wood Street, Chicago, Ill.

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EDITOR'S COLUMN

The rise in infant mortality

THE increase in man's life span in this country has been due largely to the continued decrease in infant mortality. Pediatricians and public health workers have become concerned, therefore, because the downward trend appeared to be halted in 1956, with a rate of 26.0 per 1,000 live births. In 1957 the rate increased to 26.4 and in 1958 to 26.9.* This meant the loss of approximately 113,100 infants in 1958, about 1,200 more than in 1957 and nearly 1,700 more than in 1956. In 1957 the total mortality also rose. This was generally interpreted as due to the influenza epidemic. Influenza does not seem to have played a major part in the increase in infants' deaths, however, since the infant mortality rates were higher for every month of 1958 except January and November. In 1958 the total mortality dropped (rate: 9.6 per 1,000 in 1957; 9.5 per 1,000 in 1958) while infant mortality continued to increase.

The increase in infant mortality occurred in 31 states located in all 9 geographic regions; in 2 states there was no increase and in 15 states there was a decrease. One state did not report. No particular pattern evolves from an examination of the table of rates. In the New England region, for instance, the per cent change from 1957 to 1958 was +8.3 in Connecticut and –11.5 in Maine; in the South Atlantic States it was +11.5 in South Carolina and –1.6 in Georgia; in the Mountain States it was +12.4 in Wyoming and –4.7 in Idaho. In large cities, too, the change was not all in one direction. In New York City the per cent change was +5.6; in Chicago, –1.4; in Boston, +9.0; in Baltimore –0.6.

The increased mortality rate among infants was manifest in both the neonatal (under 28 days) and the postneonatal (28 days to 11 months) periods, as can be seen in Table I.

In previous years the mortality rate for infants had decreased more rapidly in the postneonatal than in the neonatal period. In the 10 years from 1949 to 1958 the mortality rate for infants under 28 days had decreased by 9 per cent, while for infants 28 days to 11 months it had decreased by 24 per cent. In Table I it will be noted, however, that the increase from 1956 to 1958 was greater in the postneonatal than in the neonatal period (5.6 per cent as compared with 2.6 per cent).

An analysis of the causes of death is given below. It does not explain with certainty the reasons for the increases. It does allow speculation, however, and it indicates where the

Table I. Infant mortality rates per 1,000 live births

Age	*1956*	*1957*	*1958*
Under 1 year	26.0	26.4	26.9
Under 28 days	18.9	19.1	19.4
28 days to 11 months	7.1	7.3	7.5

*All data obtained from Monthly Vital Statistics Report, Annual Summary for 1958, March 12 and July 22, 1959, U. S. Department of Health, Education and Welfare, Public Health Service, National Office of Vital Statistics.

Table II. Infant mortality rates for selected causes: United States, 1949-1958 deaths under 1 year per 1,000 live births

Causes of death	*1958 (est.)*	*1957*	*1956*	*1955*	*1954*	*1953*	*1952*	*1951*	*1950*	*1949*
All causes	*26.9*	*26.4*	*26.0*	*26.4*	*26.6*	*27.8*	*28.4*	*28.4*	*29.2*	*31.3*
Certain gastrointestinal diseases	0.8	0.8	0.7	0.9	1.0	1.2	1.3	1.2	1.2	1.8
Diarrhea of the newborn	0.1	0.1	0.1	0.1	0.2	0.2	0.2	0.2	0.2	0.3
Influenza and pneumonia, except pneumonia of the newborn	2.3	2.3	2.1	2.1	2.1	2.3	2.4	2.2	2.4	2.6
Pneumonia of the newborn	0.9	0.9	0.8	0.8	0.8	0.8	0.8	0.8	0.8	0.8
Congenital malformations	3.6	3.7	3.8	3.8	3.8	3.9	3.9	3.9	4.0	4.1
Birth injuries	2.8	2.7	2.8	2.9	2.8	3.0	3.1	3.1	3.3	3.5
Postnatal asphyxia and atelectasis	4.9	4.4	4.3	4.4	4.3	4.2	4.0	4.0	3.7	3.7
Other diseases of early infancy*	2.9	2.7	2.5	2.4	2.3	2.3	2.4	2.5	2.8	3.1
Immaturity unqualified	4.6	4.9	4.9	5.3	5.4	5.8	6.0	6.2	6.3	6.6
All other causes	3.9	4.0	3.9	3.9	4.0	4.1	4.3	4.3	4.5	4.8

*Ophthalmia neonatorum, pemphigus neonatorum, umbilical sepsis, other sepsis of the newborn, erythroblastosis, hemorrhagic disease of the newborn, nutritional maladjustments, ill-defined diseases.

concentration of efforts should be placed to reduce infant mortality.

It will be noted that there has been a decline in rates for all causes in the 10 year period, except for two. The rate for one of these, pneumonia of the newborn, remained at 0.8 from 1948 to 1956, then rose to 0.9 for 1957 and 1958. The rate for the other, postnatal asphyxia and atelectasis, has been gradually increasing in the past 10 years. Three causes showed a decline in rates until 1956, then the trend was reversed. They are certain gastrointestinal illnesses, influenza and pneumonia, and other diseases of early infancy.*

In the past few years many reports have appeared of outbreaks of staphylococcal infections in nurseries for the newborn. These have accounted not only for many serious illnesses but also for a considerable number of deaths. Such deaths have been chiefly due to staphylococcal sepsis or pneumonia; these are included in categories in which the rates have increased since 1956. The increasing mortality rate during the past 10 years in the category designated as postnatal asphyxia and atelectasis requires another explanation.

The infant mortality rates for 1959 are not yet available. However, preliminary figures for the first 10 months of the year indicate a decline for the United States of 1.5 per cent since 1958. This may mean that efforts expended in organizing infection committees in hospitals, improving environmental conditions and housekeeping methods, and introducing various other procedures have been of help.

MORRIS GREENBERG, M.D., M.S.P.H.

From the Division of Epidemiology, Columbia University School of Public Health and Administrative Medicine and the Bureau of Preventable Diseases, New York City Department of Health

*Ophthalmia neonatorum, pemphigus neonatorum, umbilical sepsis, other sepsis of the newborn, erythroblastosis, hemorrhagic disease of the newborn, nutritional maladjustments, ill-defined diseases.

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Infantile autism

A CASE of infantile autism in a small girl, in whom the diagnosis was suspected during the early months of life, is described in this issue.[1] The pediatrician's suspicion was aroused by the mother's report that the baby did not smile, did not seem to like being held, and did not seem to relax when held in her mother's arms. The baby's lack of interest in her parents was so striking that she was suspected of being blind. By the last trimester of the first year, the detached, withdrawn behavior was so characteristic that a definite diagnosis of early infantile autism could be made.

An interesting observation by Lewis and Van Ferney was the brightening up of the baby that took place when she was separated from the mother and put into a stimulating environment with other adults. On return to her parents she regressed to her previous behavior.

Kanner and Lesser[2] have proposed a dual etiology for early infantile autism. It is their view that the children are genetically endowed with an inability to relate to persons in normal fashion and that this deviation is exaggerated further by the way they are handled by their parents.

The altered behavior of the patient described by Lewis and Van Ferney, when transferred from one environment to another, is consistent with the thesis that the behavior of some autistic children can be altered to a noticeable degree by the way they are handled by their parents.

The early recognition of infantile autism is the task of the physician who cares for children. Only he is in a position to see the initial changes, to make an early diagnosis, and to institute prompt therapy. Whether a stimulating parent figure will prevent infantile autism, lighten its symptoms, defer its development, or be ineffective will be known only when physicians become alert to this unfortunate ailment and do something about it.

HARRY BAKWIN, M.D.

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2. Kanner, L., and Lesser, L. I.: Early Infantile Autism, Pediat. Clin. North America **5:** 711, 1958.

Ecologic factors in neoplasms

Too often our knowledge of the natural history of disease reflects the experience of observers in regions with like climatic and cultural characteristics. Drs. O'Conor and Davies, in their article on page 524 of this issue, have called attention to one of many discrepancies which will continue to emerge as trained observers penetrate unfamiliar areas. The explanation for the prevalence of nonleukemic malignant lymphoma among African children and the curious predilection for the jaw remains to be clarified.

I have had the privilege of examining sections from several examples of the jaw lesions. They are remarkably similar in pattern and are cytologically identical with certain forms of undifferentiated lymphocytic lymphoma encountered in this country.

The bizarre "water pot" effect simulates the "starry sky" phenomenon popularized by Custer but here appears as a response to retrograde alterations in the neoplasm.

EDWARD A. GALL, M.D.